Nos. 2014-1411, -1442

In the United States Court of Appeals for the Federal Circuit

CEPHALON, INC. AND ACUSPHERE, INC.,
PLAINTIFFS-APPELLANTS

v.

ABRAXIS BIOSCIENCE, LLC AND CELGENE CORP.,
DEFENDANTS-CROSS-APPELLANTS,

ABRAXIS BIOSCIENCE, INC.,
DEFENDANT

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS, NO. 11-CV-12226, HON. RICHARD G. STEARNS, PRESIDING

BRIEF OF PLAINTIFFS-APPELLANTS CEPHALON, INC. AND ACUSPHERE, INC.

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CERTIFICATE OF INTEREST

Pursuant to Circuit Rule 47.4, undersigned counsel for Plaintiffs-Appellants Cephalon, Inc. and Acusphere, Inc. certifies the following:

1. The full name of every party or amicus represented by us is:
   Cephalon, Inc. and Acusphere, Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by us is:
   Not applicable.

3. All parent corporations and any publicly held companies that own 10% or more of the stock of any party represented by us are:
   Cephalon, Inc. is wholly owned by Cupric Holding Co., Inc., which is wholly owned by Teva Pharmaceutical Industries Ltd. No publicly held corporation owns more than 10% of Teva Pharmaceutical Industries Ltd.'s stock. Acusphere, Inc. does not have any parent corporations and no publicly traded company owns more than 10% of its stock.

4. The names of all law firms and the partners or associates that appeared for the parties now represented by us in the trial court or expected to appear in this court are:
   Winston & Strawn LLP (George C. Lombardi, Christopher B. Essig, Julia M. Johnson, William P. Ferranti, John. R. McNair, Karl A. Leonard); Goodwin Procter LLP (John T. Bennett, Nicholas K. Mitrokostas).

Dated: July 7, 2014

/s/ George C. Lombardi
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Counsel for Plaintiffs-Appellants Cephalon, Inc. and Acusphere, Inc.

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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, Plaintiffs-Appellants Acusphere, Inc. and Cephalon, Inc. state:

1. There have been no prior appeals in this case; and

2. Counsel for Plaintiffs-Appellants are aware of one related case, pending in the U.S. Supreme Court, that could affect this Court's decision in this appeal: *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, No. 13-854 (standard of review for claim construction rulings).

JURISDICTIONAL STATEMENT

This appeal arises from an action for infringement of U.S. Patent No. RE40,493 brought by Plaintiffs-Appellants Acusphere, Inc. and Cephalon, Inc. ("Plaintiffs") against Defendants Celgene Corp. and Abraxis BioScience, LLC (together, "Celgene"). The '493 patent claims an innovative way of formulating the anti-cancer drug, paclitaxel. The district court had jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338, 2201, and 2202.

On December 3, 2013, the district court entered a Memorandum and Order on Claim Construction that construed the 11 disputed terms of the claims in suit. A1–27. The court's construction of four such

terms preclude Plaintiffs from showing infringement. On that basis, on March 18, 2014, the district court entered a Stipulated Final Judgment of Noninfringement. A28–31. Consistent with this Court's directions in *Nystrom v. Trex Co.*, 339 F.3d 1347, 1351 (Fed. Cir. 2003), that Stipulated Final Judgment also ordered Celgene's counterclaims dismissed without prejudice, rendering the judgment of non-infringement final and appealable. A30.

Plaintiffs filed a timely notice of appeal on April 15, 2014. A1001–03. This Court has exclusive jurisdiction over this appeal pursuant to 28 U.S.C. § 1295(a)(1).

Celgene filed a timely notice of cross-appeal on April 22, 2014. A1004–06. Because that cross-appeal is improper, Plaintiffs moved to dismiss. Doc. 17-1. That motion was denied, but tentatively ("it appears that the cross-appeal is proper") and without prejudice to renewal in Plaintiffs' response brief. Order, Doc. 22 (June 30, 2014).

STATEMENT OF THE ISSUES

I. Whether the district court erred in construing the claim terms "**nanoparticles**" and "**microparticles**" to mean, respectively, particles with "a diameter between 1 and 1,000 nanometers (nm)," and

particles with "a diameter between 1 to 1,000 microns (μm)"—where these terms have no generally accepted, ordinary meaning, and the claims, specification, and prosecution history of the '493 patent show that the inventors used "nanoparticles and microparticles" and "microparticles" interchangeably to refer to particles having a mean diameter between about 0.01 and 5 microns (μm).

II. Whether the district court erred in construing the claim term "**nanoparticles and microparticles of a taxane**" to mean "particles formed of *only* a taxane drug" and the term "**wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles**" to mean that "the porous matrix must dissolve to leave *only* taxane drug in the form of nanoparticles and microparticles that are no longer associated with either the hydrophilic excipient or the wetting agent"—where there is no basis in the prosecution history for finding disavowal of coated particles, and this purity requirement is contradicted by the '493 patent's claims and specification, which explicitly provide for the presence of components other than naked taxane and even include a preferred embodiment involving coated taxane particles.

STATEMENT OF THE CASE

The patent-in-suit is U.S. Patent No. RE40,493, "Porous Paclitaxel Matrices and Methods of Manufacture Thereof" (issued September 9, 2008). The '493 patent claims an innovative way of formulating paclitaxel to treat patients suffering from cancer. Because Celgene has appropriated that invention and infringes the '493 patent with its drug product Abraxane®, Plaintiffs filed suit. Because the district court misconstrued four claim terms such that Plaintiffs could no longer sustain their burden of proving infringement, the parties stipulated to a final judgment of non-infringement.

A. Paclitaxel and prior art formulations

Paclitaxel is a chemical compound that occurs naturally in the Pacific yew tree, along with other trees belonging to the *Taxus* genus of coniferous trees. For decades, paclitaxel has been known to have cytotoxic (cell-killing) and anti-tumor properties. It is one of the most active agents known for treating breast and ovarian cancers. A38 col.1:18–21. Despite paclitaxel's tremendous potential in treating cancer, however, its use proved problematic. Indeed, prior art formulations of paclitaxel caused severe adverse side effects.

Those complications stemmed from paclitaxel's poor solubility in water, which made the compound difficult to administer without causing extreme discomfort. *Id.* col. 1:23–36. Since an aqueous solution appeared out of the question, the prior art turned to alternative liquid solvents—ultimately settling on Cremophor, which is 50% polyoxyethylated castor oil and 50% dehydrated alcohol. *Id.* col. 1:28–36. Cremophor can hold paclitaxel in solution, and a paclitaxel/Cremophor formulation was approved for use in patients. *Id.*

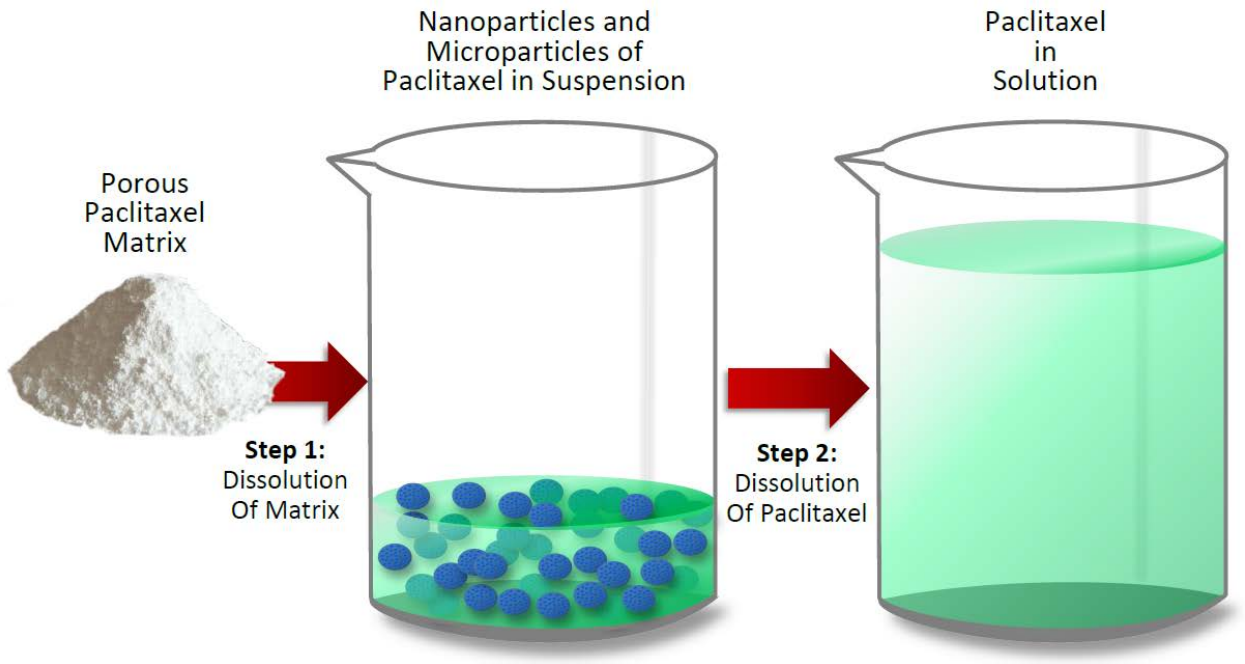
Although that formulation was effective in treating cancer, the use of Cremophor created significant secondary problems for patients. In particular, paclitaxel has a tendency to "precipitate," or solidify, out of the Cremophor solution. As a result, that formulation had to be infused into a patient slowly over the course of several hours. *Id.* col. 1:35–39. Cremophor also causes severe adverse reactions in many patients, including an allergic reaction known as hypersensitivity. To compensate for this, patients had to be treated with steroids and antihistamines before beginning the hours-long infusion of the paclitaxel/Cremophor formulation. *Id.* col. 1:39–41. Plaintiffs' invention solves these problems.

B. The '493 patent

Scientists at Acusphere, a small, research-based specialty pharmaceutical company, developed an innovative pharmaceutical composition that "dissolves more than a thousand times faster than non-formulated paclitaxel" (A2), thereby allowing the paclitaxel to be formulated without Cremophor and administered as a bolus (*i.e.*, a single, large dose). A32 at Abstract.

As set forth in the '493 patent, paclitaxel (or another taxane)[1] is put into a dry porous matrix with pharmaceutical excipients and wetting agents. Immersed in water (that is, "reconstituted" with "an aqueous medium"), the matrix dissolves, releasing paclitaxel "nanoparticles and microparticles" into suspension. Those particles are then readily dissolved when put into a larger volume of aqueous medium (as pictured below), or once administered to the patient (by injection, or after having been processed into tablets or capsules for oral administration). A32 at Abstract.

[1] Paclitaxel is defined in the specification as "includ[ing] taxanes and derivatives thereof, including paclitaxel and docetaxol …." A39 col. 3:44–49.



In this way, paclitaxel can be absorbed by a patient's body without a lengthy and uncomfortable infusion process, the use of Cremophor, or pretreatment with steroids or antihistamines. *See* A38 col. 1:66-2:1.

By overcoming such serious side effects in the prior art formulations, the '493 patent's anti-cancer formulation makes a significant advance in the treatment of cancer, particularly breast and ovarian cancer. Cancer causes nearly 25% of all deaths in this country, making it the second most common cause of death in the United States. AM. CANCER SOC., *Cancer Facts & Figures 2014*, http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/index. This year

alone, over 1.5 million Americans will be diagnosed with cancer and the disease will kill nearly 600,000. *Id.* Worldwide, over 14 million people are diagnosed with cancer each year and over 8 million die. CTRS. FOR DISEASE CONTROL AND PREVENTION, *World Cancer Day*, http://www.cdc.gov/cancer/dcpc/resources/features/worldcancerday. Fully one-third of those deaths may be preventable. *Id.*

For making this novel and useful advance, the United States Patent and Trademark Office granted the inventors a patent—specifically, U.S. Patent No. 6,610,317 (issued August 26, 2003), reissued in 2008 as the '493 patent. Acusphere granted Cephalon an exclusive license. But Celgene appropriated the patented formulation, which it sells as Abraxane®, prompting Plaintiffs to sue for infringement.[2]

C. The district court's claim constructions

Following a *Markman* hearing, the district court issued its interpretation of 11 disputed terms from the asserted claims of the '493 patent (Claims 1, 4–5, 17–19, 23, 27, 29, 45, and 47). A1–27. As pertinent

[2] Plaintiffs additionally brought suit against Abraxis BioScience, Inc. However, "based on Celgene's representation that Abraxis [BioScience, Inc.] is merely a holding company that does not manufacture, market, sell, distribute, or profit" from the accused product, the parties stipulated to its dismissal from the suit. A1 n.1.

here, however, the court incorrectly construed four terms: "nanoparticles," "microparticles," "nanoparticles and microparticles of a taxane," and "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles."

Those four terms are part of each asserted claim. Claim 1 is representative:

> A pharmaceutical composition comprising a porous matrix formed of a hydrophilic excipient, a wetting agent and **nanoparticles and microparticles of a taxane**, wherein the **nanoparticles and microparticles** have a mean diameter between about 0.01 and 5 μm and a total surface area greater than about 0.5 m^2/mL, wherein the porous matrix is in a dry powder form, and **wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles**, wherein the dissolution rate of the taxane nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed taxane.

A43 (claim terms at issue marked in bold).

Plaintiffs argued that the terms "nanoparticles," "microparticles," and "nanoparticles and microparticles of a taxane" should be construed consistent with the clear meaning of those terms as used in the '493 patent and its prosecution history. Plaintiffs further argued that the term, "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles" should be

construed consistent with its plain and ordinary meaning.

Instead, however, the court construed these terms as follows:

Claim Term	Plaintiffs' Construction	District Court's Construction
"nanoparticles"	"particles of a taxane having a mean diameter between about 0.01 and 5 µm"	particles that "have a diameter between *1 and 1000 nanometers (nm)*"
"microparticles"	"particles of a taxane having a mean diameter between about 0.01 and 5 µm"	particles that "have a diameter between *1 and 1000 microns (µm)*"
"nanoparticles and microparticles of a taxane"	"particles of a taxane having a mean diameter between about 0.01 and 5 µm"	"particles formed of *only a taxane* drug"
"wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles"	plain and ordinary meaning	"the porous matrix *must dissolve to leave only taxane drug* in the form of nanoparticles and microparticles that are *no longer associated with either the hydrophilic excipient or the wetting agent*"

See A5, 11, 17, 23, 26 (emphasis added).

These four constructions preclude Plaintiffs from carrying their burden of establishing infringement. Accordingly, the parties agreed to,

and the district court entered, a Stipulated Final Judgment of Noninfringement providing that: "The accused product does not infringe any valid claim of the '493 patent under the constructions of 'nanoparticles,' 'microparticles,' 'nanoparticles and microparticles of a taxane,' or 'wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles' rendered by this Court." A29. As explained below, however, the dispositive constructions are erroneous and, therefore, the judgment of non-infringement should be vacated.

SUMMARY OF ARGUMENT

The district court incorrectly construed the claim terms "nanoparticles," "microparticles," "nanoparticles and microparticles of a taxane," and "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles."

I. The issue with respect to "nanoparticles and microparticles" is whether the claims require the use of two different types of particles, each with a distinctly defined diameter range. The answer is clearly *no*. The terms "nanoparticles" and "microparticles" should be construed as meaning exactly what it says repeatedly in the intrinsic evidence—

particles that "have a mean diameter between about 0.01 and 5 μm."

Although it is generally understood that "nanoparticles" are smaller than "microparticles," there is no agreed-upon range of diameters applicable to each and no universally defined cut-off point between the two. The prosecution history and the patent as a whole reflect that the inventors included both terms simply to mean, *very small particles*. Beyond this, the inventors imparted precision to their claims and defined these generic terms by specifying the particles' combined *mean diameter*.

The district court acknowledged the lack of universally agreed definitions, and yet its construction *began* with extrinsic evidence that supposedly reflected a "widely accepted definition" of "microparticles" as having a range between "1 and 1000μm" and "nanoparticles" as having a range from "1 to 1000nm." A7-8 (citation omitted). Not only is this evidence the wrong starting point, but the court drew the wrong conclusions. First, it said one of the named inventors *authored* the chapter from which the extrinsic definitions proposed by Celgene were drawn, when in fact the inventor was merely the textbook's editor—which is of minimal relevance given that several other chapters in the same book

used completely different definitions. Second, the district court relied on *other* Acusphere patents that marked 1 μm as the line between "microparticles" and "nanoparticles" "as used herein." But that just suggests the inventors knew that a 1 μm line was not ordinary and did not go without saying—which cuts *against* the district court's construction.

Off on the wrong foot (both for considering extrinsic evidence in the first place, and for the conclusions it drew), the district court then determined to treat "mean diameter between about 0.01 and 5 μm" as a separate claim limitation, as opposed to the very definition of the particles in question. A9–10. The court concluded that the patent's use of two terms ("nanoparticles and microparticles") must entail the use of two distinct types of particles, but it failed to test that conclusion against the patent as a whole. In a footnote, the court acknowledged that its constructions are *impossible* to reconcile with the language of Claim 6, but it dismissed that *claim language* as "random." A9.

The court further neglected that this same "random" language is repeated in the specification, which the court also inexplicably brushed aside. Indeed, read as a whole—and particularly how it uses "microparticles" and "nanoparticles and microparticles" interchangeably—the

specification belies any notion that the inventors contemplated two distinct types of particles, each of which is separately necessary to the claimed invention. In short, the court's analysis of these claim terms is thoroughly incorrect and the resulting constructions are wrong.

The district court also misread the prosecution history, which contains *nothing* to support the court's conclusion that "formulations of the '493 patent included two separate types of particles." A10. The inventors described the prior art, and endeavored to be precise in their claims. But the inventors did not distinguish the prior art based on particle size or "type." Rather, the central distinction drawn by the inventors went to the *speed* with which the particles in the claimed invention dissolved.

Confirming the point, statements by both the inventors and the Examiner reflect an understanding that, as the Examiner put it, "nanoparticles is merely the size of a particle," and while the prior art "does not explicitly state the use of nanoparticles, [it] does teach using particles the same size as the instant invention (5μm)." A1038. Only in snippets, and not in the prosecution history as a whole, could the district court find confirmation for the flawed construction it drew from its

erroneous assessment of the extrinsic evidence. For this reason too, the district court's constructions of these terms is untenable.

II. The district court also erred by construing two other claim terms to impose a purity requirement that is unsupported by any intrinsic evidence. The patent claims a composition that begins with a matrix comprised of, among other things, "nanoparticles and microparticles of a taxane," then, "upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles …." To manufacture a non-infringement position, Celgene proposed that these terms require the use of pure taxane ("particles formed of *only* a taxane drug"), and that "the porous matrix must dissolve to leave *only* taxane drug in the form of nanoparticles and microparticles that are no longer associated with either the hydrophilic excipient or the wetting agent." A13, 26.

The '493 patent, however, never requires or in any way contemplates the use of pure taxane. To the contrary:

1. The patent describes the use of excipients that are *not* water soluble, such as magnesium aluminum silicate (A39 col. 4:61)—ingredients that, as a matter of basic science, will not

dissolve upon exposure to an aqueous medium. The patent is also explicit that the aqueous medium only dissolves "the water soluble excipients in the matrix." *Id*. col. 3:54–57.

2. The patent contains a preferred embodiment describing a "pegylated excipient" that is specifically designed to be associated with—indeed, to coat—the un-dissolved paclitaxel particles following reconstitution, so that it "beneficially envelops or shields" the taxane *in the body*. A40 col. 5:52–62. For a pegylated excipient to be associated with taxane in the body, it likewise would be associated with the taxane nanoparticles and microparticles when reconstituted in suspension prior to administration. On the district court's construction, this preferred embodiment is outside the scope of the claims.

3. The only measurement technique identified by the inventors cannot differentiate particles that are pure taxane from particles that are coated or otherwise associated with other compounds. It would be absurd if the patent claims were defined by an untestable limit.

4. The specification *repeatedly* uses the words "taxane" and "paclitaxel" where taxane or paclitaxel is the *primary*, but not the *only*, component. For example, the so-called "porous matrix of paclitaxel" or "paclitaxel matrix" (*e.g.*, A32 at Abstract) is *at most* 95% paclitaxel by weight (A39 col. 3:9–11). Likewise the "taxane" particles or particles "of a taxane" need not be 100% taxane.

The district court fared no better with the prosecution history, running afoul of the rule that disavowal may be found *only* from statements that are clear and unmistakable, as well as the rule that a patent's scope may not be cabined based on statements that merely *describe* the prior art. The court did so by accepting uncritically Celgene's mistaken contention that "the applicants made explicit that the claimed nanoparticles and microparticles of a taxane *did not encompass, controlled-release, polymer encapsulated particles containing paclitaxel and albumin*, such as was taught in the prior art." A15 (emphasis added).

In fact, the inventors merely made passing reference to "polymer encapsulate[d]" formulations in prior art references that they actually *distinguished* based not on particle purity, but rather on dissolution

rate. Further, neither the district court nor Celgene gave any reason *why* the inventors would have disclaimed this kind of formulation, which was known to be beneficial—and the prosecution history shows clearly that the inventors did not do so. The district court's contrary construction is senseless and unsupported.

STANDARD OF REVIEW

Claim construction is a question of law reviewed *de novo*. *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 744 F.3d 1272, 1276–77 (Fed. Cir. 2014) (en banc); *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc).

ARGUMENT

I. The district court erroneously construed "nanoparticles" and "microparticles."

The district court's construction of the terms "nanoparticles" and "microparticles" is based principally on extrinsic evidence, including a supposedly "widely accepted definition" of "microparticles" as having a range between "1 and 1000μm" and "nanoparticles" as having a range from "1 to 1000nm." A7-8 (citation omitted). In fact, this is *not* standard usage and the district court's analysis of the extrinsic evidence was faulty.

More fundamentally, it was error for the court to consider the extrinsic evidence in the first place—much less to *begin* with that evidence and then use it to construe these terms in conflict with the intrinsic evidence. *E.g.*, *Takeda Pharm. Co. Ltd. v. Zydus Pharm. USA, Inc.*, 743 F.3d 1359, 1363 (Fed. Cir. 2014) ("Our starting point in construing a claim term must be the words of the claim itself."); *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (the "starting point for any claim construction must be the claims themselves"); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996) ("In most situations, an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term. In such circumstances, it is improper to rely on extrinsic evidence."). By giving "microparticles" and "nanoparticles" different size limitations, and requiring that both particle "types" be present, the district court imposed a limitation that is inconsistent with the claims, specification, and prosecution history.

A. The claim language and specification dictate the proper construction of these terms.

It is a "bedrock principle" of patent law that "the claims of a patent define the invention to which the patentee is entitled …." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (citation

omitted). "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Id.* at 1316 (citation omitted).

Here, the claims and specification are clear that the inventors defined "nanoparticles and microparticles" in a particular way: particles "having a mean diameter between about 0.01 and 5 μm." The district court erred by rejecting this construction. To prevent confusion or a circumstance in which an infringer claims to use only "nanoparticles" or only "microparticles" (which is exactly what Celgene has done), the inventors referred to *both* nanoparticles *and* microparticles—and then specified the requisite particle size in terms of mean diameter.

1. There is no ordinary meaning; the inventors acted as their own lexicographer.

Everyone agrees that the only difference between a "nanoparticle" and a "microparticle" is size: both are very small, but the nanoparticle is smaller. Beyond this, as even the district court acknowledged, "*there is no universally agreed definition of the size of a nanoparticle*." A7 (emphasis added); *see also infra* 36–39; Langer Rpt. ¶28 (A1550–51); Langer Resp. Rpt. ¶28 (A1566).

But this lack of ordinary meaning is of no moment because what the inventors meant is right there in the claim language: Claim 1 uses "nanoparticles and microparticles of a taxane, wherein *the nanoparticles and microparticles have a mean diameter between about 0.01 and 5 μm* and a total surface area greater than about 0.5 m^2/mL." A43 (emphasis added); *see also* Langer Rpt. ¶¶ 29–30 (A1551–52); Langer Resp. Rpt. ¶27 (A1566). Accordingly, "nanoparticles" and "microparticles" should be construed as "particles having a mean diameter between about 0.01 and 5 μm."

To the extent this definition differs from accepted usage (and, again, for these terms, there is no such thing), the specification makes clear that the inventors acted as their own lexicographers. Courts should adopt the patentee's definition where "the patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term in … the specification." *Edwards Lifesciences LLC v. Cook Inc.*, 582 F.3d 1322, 1329 (Fed. Cir. 2009) (citation omitted). "The specification acts as a dictionary when it expressly defines terms used in the claims *or when it defines terms by implication*." *Vitronics*, 90 F.3d at 1582 (emphasis added).

The district court here concluded that "there is very little evidence in the disputed patent … to suggest that Acusphere left a Websterian imprint on the '493 patent" because, "[w]hile the '493 patent defines other terms in a definitional format …, it does not formally define nanoparticles or microparticles." A8.

As a matter of law, however, patentees are not required to explicitly define terms in a dictionary format in order to act as a lexicographer. The specification may define terms by implication. *E.g.*, *Vitronics*, 90 F.3d at 1582; *see also Bell Atl. Network Servs., Inc. v. Covad Commc'ns Grp., Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001) (if a patentee uses a claim term "throughout the entire patent specification, in a manner consistent with only a single meaning, he has defined that term 'by implication'"). And, when they do define certain terms in a dictionary format, that is no reason to conclude that they acted as a lexicographer with respect to *only* those specific terms.

Here, the inventors plainly *did* define the terms "nanoparticles" and "microparticles" in the '493 patent. The specification and the claims repeatedly use "microparticles" and "nanoparticles and microparticles" to mean particles that "have a mean diameter between about

0.01 and 5 μm." A38 col. 1:65–2:4; A43, claim 1; A44, claims 17, 37, and 41. No other construction is consistent with this evidence or the other intrinsic evidence discussed below.

The district court reasoned that the "mean diameter" language must be treated as a "separate limitation" (as opposed to the very definition of "nanoparticles and microparticles") because the subsequent phrase ("and a total surface area greater than about 0.5 m^2/mL") is without doubt a separate limitation. A9–10. But, as the court itself acknowledged, microparticles and nanoparticles are "distinguish[ed] … by their size" and there is no "evidence that surface area has ever been used to define the terms." A10. It thus makes perfect sense that mean diameter would define the requisite particles, while total surface area would not. In other words, Plaintiffs' proposed construction "naturally aligns with the patent's description of the invention." *Phillips*, 415 F.3d at 1316 (citation omitted).

2. The district court's construction is indisputably impossible to reconcile with Claim 6.

Further, Plaintiffs' proposed construction—unlike the district court's—"stays true to the claim language." *Phillips*, 415 F.3d at 1316. Dependent Claim 6 covers "[t]he composition of claim 1 wherein the

mean diameter of the taxane *microparticles* is between about *0.50 and 5 μm*." A43 (emphasis added). The district court drew a bright line at 1 μm (1000 nm)—with "nanoparticles" being smaller than this, and "microparticles" larger. But it would be impossible to have a population of microparticles, each larger than 1 μm (as required by the district court's construction) yet having collectively a mean diameter as low as 0.50 μm (as Claim 6 expressly provides). *See also* A38 col. 2:1–5 (specification) (referring to "*microparticles* having a mean diameter between about *0.01 and 5 μm*") (emphasis added); A39 col. 3:15-18 (specification) (referring to "*microparticles* … which preferably have a diameter between about *10 nm and 5 μm*") (emphasis added). The claim language and specification thus make clear that "nanoparticles and microparticles" and "microparticles" refer to the same particles.

Incredibly, the district court acknowledged this problem, *i.e.*, that Claim 6 calls for "microparticles" with a mean diameter that is *impossible* to achieve under its construction. A9 n.2. But the court attributed this "inconsistency" to the inventors' "at times seemingly random omission of the term 'nanoparticles' in the patent." *Id.* The gravity of this error is difficult to overstate. The "starting point in construing a claim

term must be the words of the claim itself," *Takeda Pharm.*, 743 F.3d at 1363, but here, the district court dismissed the *claim language* (and corresponding statements in the specification) as "random," thereby lopping off a chunk of Claim 6 (the part specifying a mean diameter between 0.5 and 0.99 μm), and creating an "inconsistency" that is absurd and entirely unnecessary.

The resulting construction cannot stand. *See Rambus Inc. v. Infineon Techs. AG*, 318 F.3d 1081, 1093 (Fed. Cir. 2003) ("The district court's construction would render claim language in dependent claims 27 and 28 meaningless. This court disfavors such a construction."); *Marine Polymer Techs., Inc. v. HemCon, Inc.*, 672 F.3d 1350, 1368 (Fed. Cir. 2012) ("Where a particular construction of an independent claim would nullify claims that depend from it, the doctrine of claim differentiation creates a presumption that such a construction is improper."); *Gen. Am. Transp. Corp. v. Cryo-Trans, Inc.*, 93 F.3d 766, 770 (Fed. Cir. 1996) (reversing district court's claim construction which "obliterated" a claimed structural distinction).

3. The specification further compels Plaintiffs' construction.

The district court's construction is also impossible to square with the specification. The specification "is the single best guide to the meaning of a disputed term." *Vitronics*, 90 F.3d at 1582. It should be considered as a whole, with all portions of the written description read, to the extent possible, in a manner that renders the patent internally consistent. *ArcelorMittal France v. AK Steel Corp.*, 700 F.3d 1314, 1320 (Fed. Cir. 2012) (citing *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 429 F.3d 1364, 1373 (Fed. Cir. 2005)); *Budde v. Harley-Davidson, Inc.*, 250 F.3d 1369, 1379-80 (Fed. Cir. 2001).

Here too, the district court failed. The specification does not contemplate two different particle types, nor does it define "nanoparticle" separately from "microparticle." Indeed, the specification *never* refers to "nanoparticles" alone (nor do the claims). But the specification does refer to "microparticles"—as opposed to "nanoparticles and microparticles"—and this shorthand confirms the district court's error.

Take, for example, the first two sentences of the "SUMMARY OF THE INVENTION":

> Paclitaxel is provided in a porous matrix form which forms *nanoparticles and microparticles* of paclitaxel when the matrix is contacted with an aqueous medium. The porous matrix with paclitaxel yields upon contact with an aqueous medium *microparticles* having a mean diameter between about 0.01 and 5 μm and a total surface area greater than about 0.5 m^2/mL.

A38 col. 1:65–2:5 (emphasis added). The second sentence adds precision, but both sentences are plainly referring to the same thing—the particles that result from the matrix coming into "contact[] with an aqueous medium." The inventors refer to such particles interchangeably as "nanoparticles and microparticles" (the first sentence above) or just "microparticles" (the second sentence). *Also compare* A39 col. 3:1-3 ("upon the addition of an aqueous medium," the porous dry powders "form a suspension of paclitaxel *nanoparticles and microparticles*"), *with id.*, col. 3:15-16 ("upon contact with an aqueous medium," the matrix "must yield *microparticles* of paclitaxel") (emphasis added); *see also* Langer Rpt. ¶¶ 29–30 (A1551–52).

Moreover, the specification *twice* squarely refers to *microparticles* with a diameter between *0.01 and 5 μm*. A38 col. 2:3-4 ("microparticles having a mean diameter between about 0.01 and 5 μm"); A39 col. 3:15-17 ("microparticles … which preferably have a diameter between about

10 nm and 5 μm"). Like Claim 6 (discussed above), the specification thus flatly contradicts the district court's construction of "microparticles" as particles having a diameter between 1 and 1,000 μm.[3]

4. The district court gave undue weight to the word "and" and failed to test its construction against the patent as a whole.

Just as it paid too little regard to the claim and specification language just discussed, the district court also moved too quickly with respect to the word "and." The court reasoned that, "if 'nanoparticles *and* microparticles' are defined indistinguishably by their mean diameter, the population could theoretically be comprised entirely of nanoparticles *or* microparticles, contrary to the conjunctive language of the claim." A6. But while "and" is *usually* conjunctive, it is not necessarily so. The fact that the patent says "nanoparticles *and* microparticles" instead of "nanoparticles *and/or* microparticles" cannot end the analysis.

In situations where it is clear that the inventors intended a dis-

[3] The district court quoted the same two sentences set forth above, from the outset of the SUMMARY OF INVENTION, even adding emphasis to the portion reading, "*microparticles having a mean diameter between about 0.01 and 5 μm*." A9 (quoting and adding emphasis to A38 col. 1:66–2:5). But the court dismissed this language with the baffling remark that, "the only sentence [*sic*] that Acusphere can point to in the specification as supporting a definition by inference, does not even mention nanoparticles." A9.

junctive meaning, courts refuse accused infringers' efforts to narrow a patent's claims. *E.g.*, *Allergan, Inc. v. Apotex Inc.*, No. 2013-49, 2014 WL 2579287, at *3 (Fed. Cir. June 10, 2014) (affirming conclusion that claim language "arresting hair loss, reversing hair loss, or both *and* promoting hair growth" may include a method of promoting hair growth without also arresting or reversing hair loss" in view of "the patentee's own lexicography in light of the whole specification") (emphasis added); *Joao v. Sleepy Hollow Bank*, 348 F. Supp. 2d 120, 123-25 (S.D.N.Y. 2004), *aff'd sub nom*, *Joao Bock Transaction Sys., LLC v. Sleepy Hollow Bank*, at 445 F. App'x 359 (Fed. Cir. 2011) (reading "and" in claim language as "or" because, although "the plain meaning of the language is conjunctive, not disjunctive," in "test[ing] … by referring to the specifications … it becomes clear that the patentee did not intend to use the phrase in its plain and ordinary way") (citing *Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1578 (Fed. Cir. 1996)); *Thomson Consumer Elecs., Inc. v. Innovatron, S.A.*, 43 F. Supp. 2d 26, 34-35 (D.D.C. 1999) ("the Court is persuaded that one skilled in the art would read 'non-alignment *and* non-existence of electric contact' to mean 'non-alignment *or* non-existence of electric contact'") (emphasis added) (citing

Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1250 (Fed. Cir. 1998) ("Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventor actually invented and intended to envelop with the claim.")).

Here too, while the claim perhaps could have used "or" rather than "and," the district court should have tested its "ordinary meaning" interpretation against the patent as a whole. But it did not. Instead, it dismissed the language of Claim 6 as "random," ignored the parts of the specification that undercut its construction, and ultimately failed to adopt the construction that stayed "true to the claim language and most naturally aligns with the patent's description of the invention." *Phillips*, 415 F.3d at 1312.

The district court's construction also creates a ready "out" for infringers like Celgene. By asserting that they use "microparticles" or "nanoparticles" (but not both!) a party can exploit Plaintiffs' invention without fear of an infringement finding, even if they use a collection of very small particles with "a mean diameter between about 0.01 and 5 μm." That is exactly what the district court's construction has allowed Celgene to do here. If the court had properly analyzed the claim lan-

guage, the specification, and the prosecution history, it would not have allowed its *Markman* order to create a roadmap for liability-free exploitation of the '493 patent's invention. By referring to both "nanoparticles and microparticles," the inventors just meant that their claims covered any mix of very small particles having the specified mean diameter.

B. The prosecution history establishes that the inventors did not mean, and the Examiner did not understand, "nanoparticles" as a second, distinct type of particle.

The district court also misinterpreted the prosecution history.

First, the court erroneously concluded that the inventors' "position before the PTO was that the formulations of the '493 patent included two separate types of particles, characterized by their size." A10. That conclusion is baseless. Attempting to be clear, the inventors added "nanoparticles and" to the claim language, and referred to "nanoparticles and microparticles" in correspondence with the Examiner. But they never changed the size range claimed, and it is clear (as further shown below) that the Examiner did *not* understand "nanoparticles" and "microparticles" to be two distinct types of particle. A1038. Nor is there anything in the prosecution history to support the notion that the claimed invention requires the use of two distinct types of particles.

Second, it is also incorrect that the inventors distinguished the prior art formulations based on particle size. *Contra* A10. Instead, the prosecution history shows that the inventors and the Examiner both recognized that particle size did *not* distinguish the prior art.

The relevant portion of the prosecution history relates to the Examiner's rejection of the inventors' application as obvious in light of two references, Desai and Hanes. A1011. According to the Examiner, Desai taught "compositions and methods for the in vivo delivery of pharmacologically active agents (such as paclitaxel)" and further taught the use of "matrices," while Hanes added the use of a surfactant. A1011–12. The Examiner thus preliminarily concluded that "a composition, and methods for making such, containing paclitaxel and a surfactant, in micron size and with a reduced surface area would have been known to one with ordinary skill in the art." A1012.

The district court seized on the Examiner's reference to "in micron size." *See* A6. But while "the precedent of this court indicates that a patentee's remarks during patent prosecution can illuminate the meaning of the claims …, [it] makes equally clear that this court construes an administrative record in its full context, not on the basis of snippets

lifted out of context." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1576 (Fed. Cir. 1997) (citation omitted).

Here, the Examiner's rejection was not centered on particle size specifically. And, moreover, the inventors responded to this Office Action by distinguishing the prior art based on *dissolution rate*, not particle size. They *described* Hanes by saying, among other things, "There are no nanoparticles…." A1021. But to *distinguish* the prior art, they explained:

> Hanes and Desai in combination would not lead one skilled in the art to a formulation that *dissolves almost immediately upon administration*, to make the drug available *more rapidly*. Rather, the combination would lead one to *controlled, sustained release formulation* for pulmonary administration, where the drug formulation had a total particle size of less than five microns, not a formulation having dispersed therein nanoparticles and microparticles of drug, *released immediately upon dissolution of the surrounding matrix.*

Id. (emphasis added). The inventors thus squarely acknowledged that the prior art pointed to a formulation with "a total particle size of less than five microns" (*id.*)—which was the *same* as their invention. Further, and at the same time, the inventors tweaked their nomenclature ("microparticles" became "nanoparticles and microparticles"), but they did not change the size range (always, 0.01 to 5 μm). A1016; *see also*

Langer Resp. Rpt. ¶36 (A1569–70). The addition of "nanoparticles" was a matter of semantics, not substance.

And the Examiner demonstrated that he shared this understanding that "nanoparticles" merely referred to the specified particles, *i.e.*, those having a mean diameter between about 0.01 and 5 μm: "it is the examiner's understanding that nanoparticles is merely the size of a particle, and whereas Hanes does not explicitly state the use of nanoparticles, Hanes does teach using particles the same size as the instant invention (5μm)." A1038. Thus the Examiner clearly did *not* understand that the terms "nanoparticles" and "microparticles" were distinguished in the '493 patent by size.

Throughout the prosecution history, the inventors focused on dissolution rate. A1045–47. They clarified that "Hanes discloses large diameter (*i.e.*, greater than 5 μm) aerosolizable particles for pulmonary administration." A1046. Thus, to the extent particle size distinguished the invention from Hanes in particular (as opposed to the combination of Desai and Hanes, which the inventors had previously acknowledged might point to particles "less than five microns," A1021), it was not because there are "nanoparticles" and "microparticles"; it was because the

inventors were using particles (whatever called) of less than 5 μm in diameter.

The Examiner accepted the inventors' argument, stating that the "most notabl[e]" point which "overc[a]me the teachings of the prior art" was the fact that "the dissolution rate of the taxane nanoparticles and microparticles … is increased relative to unprocessed taxane." A1060.

Further, and critically, even to the extent size was a basis for distinguishing the prior art, it is not correct that the inventors took the position "that the formulations of the '493 patent included two separate types of particles, characterized by their size." A10. This is the district court's central error. Again, there is *nothing* in the prosecution history about "two separate types of particles."

In sum, prosecution history is important because it "provides evidence of how the PTO and the inventor understood the patent." *Phillips*, 415 F.3d at 1317. Here, the inventors' submissions and the Examiner's responses show that the pivotal difference between the invention and the prior art was that the claimed particles dissolved more quickly than what was disclosed in the prior art. The size of the particles did not distinguish the invention from the prior art because, as the Exam-

iner explained, "whereas Hanes does not explicitly state the use of nanoparticles, Hanes does teach using particles the same size as the instant invention." A1038.

By failing to assess the prosecution history in its "full context" and construing the claim terms instead "on the basis of snippets lifted out of context," *J.T. Eaton & Co.*, 106 F.3d at 1576, the district court erred. Worse, the district court did not even use the snippets so much for purposes of construction as for purported confirmation of the construction it had already drawn from its improper and erroneous reliance on extrinsic evidence.

C. The district court's reliance on extrinsic evidence was flawed and improper.

In ruling that the '493 patent "relies on the widely accepted definition propounded by Celgene," the district court wrongly relied on two pieces of extrinsic evidence: (1) a 1996 textbook allegedly "co-authored by Howard Bernstein, one of the named inventors on the '493 patent," and (2) "other [of Plaintiffs'] patents" that "incorporate the definition taught by" the textbook. A7–8.

As to the first, the district court was undeniably mistaken in stating that the textbook in question, *Microparticulate Systems for the De-*

livery of Proteins and Vaccines (Smadar Cohen and Howard Bernstein eds. 1996), was "co-authored" by a named inventor. A7. The fact is, the inventor—Howard Bernstein—was an *editor* of the textbook. He did not *author* the chapter in question. That chapter was authored by Thomas Kissel and Regina Koneberg of Philipps University in Germany. A1303. There is no evidence suggesting that Dr. Bernstein provided any input for the range of particle sizes defined in that chapter.

Moreover, this same chapter noted: "The term *microspheres*, or *microparticles*, is sometime[s] used rather liberally in the literature to describe particulate-delivery systems, *irrespective of size* …." A1308, *Microparticulate Systems* at 61 (final emphasis added).

Other sections of this textbook likewise demonstrate that, contrary to the district court's interpretation, skilled artisans often consider particles of less than 1 μm to be "*microparticles*," not nanoparticles, and particles of greater than 1 μm to be "*nanoparticles*," not microparticles. For example, the authors of chapter 3 refer to "microparticles (< 1 – 2 μm)" (A1330) and report on tests involving microparticles in which "10% were smaller than 1 μm" (A1335). The author of chapter 7 refers to a population of *nanoparticles*, "with a mean size of 1 μm" (A1385), while

at the same time citing an article about "[t]he preparation of sub-200 nm … *microspheres*." A1396 n.50. The authors of chapter 12 also part company with the district court, referencing a study involving *microparticles* that were "smaller than 100 nm in diameter …." A1461. And the authors of chapter 13 refer to microparticles "of … 0.05 μm." A1474.

In fairness, still other authors applied a definition similar to the one proposed by Celgene and adopted by the district court. *E.g.*, A1418; A1471. But that just proves the point: there is no agreement in the field as to the delineation between nanoparticles and microparticles.

Equally misplaced is the district court's assertion that "other Acusphere patents" adopted the definition from the textbook chapter discussed above. A8. In fact, those patents did not cite the book chapter; they just drew a line at 1 μm to define the size of "microparticles" and "nanoparticles" "*as used herein*." *See* A1113 (emphasis added); A1138; A1177; A1207–08; A1235. Tellingly, however, that is not what the inventors did in the '493 patent. Rather, as shown above, they defined their particles in terms of a mean diameter. Juxtaposing these patents and the '493 patent thus betrays and does not confirm the district court's construction.

In short, the extrinsic evidence is meaningless at best. "[W]hile extrinsic evidence 'can shed useful light on the relevant art,' we have explained that it is 'less significant than the intrinsic record in determining the legally operative meaning of claim language.'" *Phillips*, 415 F.3d at 1317 (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.,* 388 F.3d 858, 862 (Fed. Cir. 2004)). This is so because "[t]he claims, specification, and file history, rather than extrinsic evidence, constitute the public record of the patentee's claim, a record on which the public is entitled to rely…. Allowing the public record to be altered or changed by extrinsic evidence … would make this right meaningless." *Vitronics*, 90 F.3d at 1583. Yet, that is exactly what the district court did here.

II. The district court erroneously added a "taxane only" requirement to the claims.

The district court also misconstrued two other claim terms by improperly adding a limitation requiring the use of pure taxane particles. A11–17. Again looking to Claim 1 as representative, the '493 patent claims "[a] pharmaceutical composition comprising a porous matrix formed of a hydrophilic excipient, a wetting agent and **nanoparticles and microparticles of a taxane** … and wherein upon exposure to an aqueous medium, the matrix dissolves to leave the **taxane nanoparti-**

cles and microparticles ...." A43 at Claim 1 (emphasis added).

According to the district court, the use of "taxane" as an adjective or object of a preposition—as in, "nanoparticles and microparticles *of a taxane*" and "*taxane* nanoparticles and microparticles"—imposes a strict purity requirement such that "the porous matrix must dissolve to leave only taxane drug in the form of nanoparticles and microparticles that are no longer associated with either the hydrophilic excipient or the wetting agent." A26. As shown below, this is wrong.

First and foremost, the district court misread the claim language and specification. The patent does not require purity. To the contrary, it describes and claims formulations in which the taxane is *necessarily* linked with other components, including a preferred embodiment in which the taxane is *coated*. The district court, however, ignored scientific fact and adopted a construction that excises from the patent this preferred embodiment.

Second, the district court misread the prosecution history. This Court has repeatedly warned that "[p]rosecution disclaimer does not apply … if the applicant simply describes features of the prior art and does not distinguish the claimed invention based on those features."

E.g., *Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008). Here, however, the district court seized on the inventors' *description* of prior art involving polymer encapsulated formulations, ignoring—indeed, carving up its quotations from the prosecution history to omit—that the inventors actually *distinguished* that prior art on the ground that it "would not lead one skilled in the art to a formulation that dissolves almost immediately upon administration." A1021.

A. The claims and specification foreclose the district court's construction.

The district court concluded that, because "[a]ll limitations in a claim must be considered meaningful, … the court construes the term 'of a taxane' to mean 'particles formed *of only* a taxane drug." A16–17 (internal citation and quotation marks omitted). But the court's conclusion does not follow from its premise.

The claims consistently refer to "the taxane nanoparticles and microparticles" and "the nanoparticles and microparticles of a taxane." They *do not* recite "pure taxane" nanoparticles and microparticles or "100% taxane" nanoparticles and microparticles, or nanoparticles and microparticles of "only" a taxane. They also do not recite that the taxane particles must be free of all other components in the composition, or

that reconstitution in an aqueous medium must leave nanoparticles and microparticles that contain only taxane. Nor does the patent anywhere teach or reference any purification step or process. The district court's construction thus improperly reads into the claims a purity limitation that is not there. *See Solvay S.A. v. Honeywell Int'l, Inc.*, 622 F.3d 1367, 1382 (Fed. Cir. 2010) (rejecting construction of "isolating" to mean that *only* the desired composition could be present); *DSW, Inc. v. Shoe Pavilion, Inc.*, 537 F.3d 1342, 1348 (Fed. Cir. 2008) (courts may not "improperly read into [claims] a new limitation not required by the claim language, specification, or prosecution history").

And the district court's construction is belied not only by what the patent does not say, but also by what it does.

First, the indisputable scientific fact is that, when certain claimed matrices dissolve (*i.e.*, are reconstituted in an aqueous medium), pure taxane is not left alone in suspension. It couldn't be.

Claim 1 provides that "nanoparticles and microparticles of a taxane" are initially part of a dry porous matrix that subsequently "dissolves to leave the taxane nanoparticles and microparticles." A43. That matrix is made up of "at least 1 to 95% taxane by weight" and "al-

so may contain hydrophilic excipients such as water soluble polymers and sugars, wetting agents such as surfactants, and tonicity agents." A39 col. 3:9–14. The specification further provides examples of "wetting agents" that are not water soluble, including magnesium aluminum silicate. A39 col. 4:40–61; A12.

The claims must be read consistent with basic science: components of the matrix that are not water soluble will not dissolve; they will be left in suspension. Accordingly, the "taxane nanoparticles and microparticles" left in suspension after the matrix dissolves are not necessarily pure taxane. Confirming the point, the specification explains: "Upon contact with an aqueous medium, water penetrates through the highly porous matrix to dissolve *the water soluble excipients* in the matrix." A39 col. 3:54–57.

Thus, the patent shows on its face that there may be excipients or wetting agents in the matrix that do not dissolve and that, therefore, would *necessarily* be present once "the matrix dissolves to leave the taxane nanoparticles and microparticles."

Second, the '493 patent includes a preferred embodiment in which "the matrix further includes a pegylated excipient" which "bene-

ficially envelops or shields the paclitaxel from macrophage uptake, which prolongs its half-life or enhances bioavailability of the compound." A40 col. 5:52–62. This "envelop[ing] or shield[ing]" is a benefit *in the body—after* the dry porous matrix has been reconstituted to leave in suspension "taxane nanoparticles and microparticles." According to the district court, that reconstitution step (the dissolution of the matrix) must dissolve everything else and leave only 100% pure taxane particles. According to the '493 patent, however, a preferred embodiment is envisioned where the "taxane nanoparticles and microparticles" are not naked and pure as the district court requires, but coated.

In other words, the district court's construction means that a preferred embodiment of the '493 patent is outside the scope of the patent's claims. As the Court said in *Vitronics*, 90 F.3d at 1583, so too here: "Such an interpretation is rarely, if ever, correct and would require highly persuasive evidentiary support, which is wholly absent in this case." *See also Invitrogen Corp. v. Biocrest Mfg., L.P.,* 327 F.3d 1364, 1369 (Fed. Cir. 2003) (district court's claim construction erroneously excluded an embodiment described in an example in the specification).

Third, the only testing method disclosed in the intrinsic evidence is not capable of distinguishing between particles of taxane and other particles.[4] Using that method—a Coulter Counter—it would be impossible to measure whether taxane is all that is present after the matrix dissolves. *See* Langer Resp. Rpt. ¶41 (A1571). The district court's construction thus supposes a significant limitation for which the inventors provided no test. A claim construction that yields such an absurd result cannot be correct. *AIA Eng'g Ltd. v. Magotteaux Int'l S/A*, 657 F.3d 1264, 1276 (Fed. Cir. 2011) (courts "strive, where possible, to avoid nonsensical results in construing claim language").

Fourth, further confirming that "taxane" and "of taxane" does not mean "*only* taxane," the specification *repeatedly* uses the words "taxane" and "paclitaxel" where taxane or paclitaxel is a *significant*, but not the

[4] The '493 patent derives from United States Provisional Application No. 60/158,659 ("the '659 provisional application"). A39. The '659 provisional application, therefore, is part of the intrinsic record. *E.g.*, *EveryScape, Inc. v. Adobe Sys., Inc.*, No. 10-11597, 2012 WL 5389735, at *4-5 (D. Mass. Nov. 5, 2012); *Chi. Mercantile Exch., Inc. v. Tech. Research Grp., LLC*, 721 F. Supp. 2d 785, 793-94, 800 (N.D. Ill. 2010). The '659 provisional application discloses a "Coulter Counter" as the measurement method. A1070, 1088. A Coulter Counter measures *size*, but does not distinguish between *types* of particles.

only, component.[5] For example, the specification refers to "the paclitaxel solution" and the "paclitaxel solvent," which are paclitaxel and a volatile solvent—not 100% pure paclitaxel. A38 col. 2:8–9, 18, 22–23, 29; A41 col. 7:40–43. Similarly, the patent characterizes the matrix as a "porous matrix of paclitaxel" or "paclitaxel matrix"—but the matrix is *at most* 95% paclitaxel by weight. A32 (Abstract); A38 col. 2:13; A39 col. 3:8, 9–11, 24; A41 col. 7:26–27; A42 col. 10:60. Likewise, when the patent refers to a particle "of taxane," it is not referring to 100% pure taxane, but to a particle the significant part of which is taxane.

In sum, nothing in the patent requires, or even suggests, that pure taxane be used in, or emerge from dissolution of, the dry matrix. Quite the opposite. Accordingly, the district court erred by adding this limitation to the claims. *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 339 (1961) ("[T]he claims made in the patent are the sole measure of the grant."); *McCarty v. Lehigh Valley R.R. Co.*, 160 U.S. 110, 116 (1895) ("[I]f we once begin to include elements not mentioned in the claim, in order to limit such claim, … we should never know where to stop."); *Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324,

[5] As used in the '493 patent, "paclitaxel" "includes taxanes and derivatives thereof, including paclitaxel and docetaxol." A39 col. 3:44–49.

1330 (Fed. Cir. 2012) (rejecting attempt to add limitations where "[n]either the claims, the specification, nor the prosecution history suggest that the claimed perfusion must satisfy certain safety or efficacy standards."); *Rambus Inc. v. Infineon Techs. AG*, 318 F.3d 1081, 1088 (Fed. Cir. 2003) ("[C]ourts may not read limitations into the claims."); *N. Telecom Ltd. v. Samsung Elecs. Co., Ltd.*, 215 F.3d 1281, 1290 (Fed. Cir. 2000) ("This court has repeatedly and clearly held that it will not read unstated limitations into claim language.").

B. The prosecution history does not show disavowal.

Nor does the prosecution history support the district court's construction. The district court relied heavily on what it called the inventors' "effort to escape the teachings of Desai and Hanes." A16. In point of fact, the inventors did not try to "escape" any prior art teachings; they explained the ways in which their invention differed. And those differences had nothing to do with whether the prior art or claimed formulations contained pure taxane. Rather, as described above (at 31–36), the inventors distinguished the Hanes and Desai references based on *dissolution rate*, not particle purity.

Following the Examiner's initial rejection, the inventors characterized the prior art as follows:

> Hanes discloses a formulation that has two embodiments, one formed of a biodegradable hydrophobic, non-water-soluble polymer encapsulating drug, which can include a surfactant … and the other just of drug and surfactant …
>
> Desai discloses **controlled release**, polymer encapsulated formulations. Desai teaches away from anything that would **dissolve almost immediately** upon administration, to release drug in particulate form.
>
> Accordingly, Hanes and Desai in combination would not lead one skilled in the art to a formulation that **dissolves almost immediately** upon administration, to make drug available **more rapidly**. Rather, the combination would lead one to **controlled, sustained release** formulation for pulmonary administration, where the drug formulation had a total particle size of less than five microns, not a formulation having dispersed therein nanoparticles and microparticles of drug, **released immediately upon dissolution** of the surrounding matrix.

A1021 (quoted in part at A14) (emphasis added). The district court ignored the clear thrust of the inventors' distinguishing of the prior art—reflected in the string of bolded words above.

Instead, quoting the first two paragraphs excerpted above, but omitting the third, the district court accepted Celgene's argument that "the applicants made explicit that the claimed nanoparticles and microparticles of a taxane *did not encompass, controlled-release, polymer en-*

capsulated particles containing paclitaxel and albumin, such as was taught in the prior art." A15 (emphasis added). But, while it just so happens that Celgene's infringing product is encapsulated with albumin, the inventors said no such thing. The statements on which the district court focused were not directed at distinguishing the claimed nanoparticles and microparticles from the prior art; they were merely descriptive of the prior art as a whole. *See Shire Dev. LLC v. Watson Pharm. Inc.*, 746 F.3d 1326, 1332 (Fed. Cir. 2014) ("During prosecution, Shire carefully characterized the *prior art* as not having separate matrices but never actually stated that the *claimed invention does have* separate matrices.").

At the same time, the inventors distinguished their own invention from that prior art:

> The matrix is rapidly dissolved upon contact with an aqueous solution, yielding nanoparticles and microparticles of the taxane, *no longer associated with the matrix.* The nanoparticles and microparticles of the taxane lead to an increase[d] rate of dissolution of the taxane.

A14 (quoting prosecution history at A1021) (emphasis added by the district court). In responding to the Examiner's second rejection, the inventors further explained:

> The combination of Desai and Hanes would not lead one skilled in the art to form a porous matrix which dissolves immediately upon exposure to an aqueous medium to release *nanoparticles and microparticles of a taxane that have a high surface area and dissolve rapidly*.

A15 (quoting and adding emphasis to prosecution history at A1046).

Contrary to the district court's assessment (A16–17), these statements in no way suggest a "taxane only" requirement. Rather, the inventors' message to the Examiner was that their invention differed from Desai and Hanes in that the nanoparticles and microparticles dissolved much more rapidly than was taught in the prior art. Indeed, as they pointed out, the prior art taught that it was "critical to have [the taxane particles] remain in suspension…" *in vivo*. *See, e.g.*, A1046. The inventors simply did not speak to whether the taxane particles that dissolve are pure taxane.

To be sure, the inventors characterized the prior art (both Hanes and Desai) as involving "polymer encapsulating" formulations. A1021; A1046 (pertinent excerpt quoted above). But "prosecution disclaimer does not apply … if the applicant simply describes features of the prior art and does not distinguish the claimed invention based on those features." *Computer Docking*, 519 F.3d at 1375; *see also, e.g.*, *Shire*, *supra*;

Cohesive Techs., Inc. v. Waters Corp., 543 F.3d 1351, 1361 (Fed. Cir. 2008) ("In this case, the Guiochon declaration does not distinguish the … particles because they are polymeric; instead, it distinguishes the particular polymeric materials taught in Afeyan … because "*[s]uch* polymeric materials" are not sufficiently rigid when exposed to the relevant level of pressure. The Guiochon declaration may, therefore, be a clear and unmistakable disavowal of the *particular* particles used in Afeyan, but it is not a disavowal of *all* polymeric particles."); *Eolas Techs. Inc. v. Microsoft Corp.*, 399 F.3d 1325, 1337 (Fed. Cir. 2005) (no disclaimer where, although "the applicants included language about [the alleged disclaimed features] in their response, they did not distinguish the … invention based on these features").

When they distinguished their own formulations from the prior art, the inventors called out the speed of dissolution of the taxane nanoparticles and microparticles. *E.g.*, A1045–47. The issue was not coated or uncoated; it was that, Desai, for example, "disclose[d] controlled release, polymer encapsulated formulations," and thereby "teaches away from anything that would dissolve immediately"—as compared to their own invention, "a rapidly dissolving preparation of taxane nanoparti-

cles." A1021, A1045–47. In contrast, the prior art "discloses taxane which is not soluble, but which is in a matrix that dissolves to leave insoluble taxane microparticles in the form of a colloidal suspension." A1045.

The district court did not explain its leap from what the inventors actually said to a purity requirement. Nor did it make any effort to discern a reason *why* the exclusion of a polymer encapsulation would (or wouldn't) make sense here. Nothing in the patent, the prosecution history, or the expert reports indicates that the claimed invention would need to use uncoated taxane.

Instead of explaining its reasoning, the district court merely summarized the parties' arguments and dismissed Plaintiffs' as "unconvincing at the least." A16. Plaintiffs respectfully disagree. This Court has repeatedly held that the burden for showing a disclaimer of claim scope via prosecution history is high: it requires "expressions of manifest exclusion or restriction … representing a clear disavowal of claim scope," and "that the alleged disavowing actions or statements made during prosecution be both clear and unmistakable." *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002); *Omega Eng'g*

Inc. v. Raytek Corp., 334 F.3d 1314, 1325-26 (Fed. Cir. 2003); *see also Vederi LLC v. Google, Inc.*, 744 F.3d 1376, 1384 (Fed. Cir. 2014) ("This statement does not give rise to a clear and unmistakable disavowal."); *Shire*, 746 F.3d at 1331 ("the doctrine of prosecution disclaimer only applies to unambiguous disavowals") (citation omitted).

This standard is not met in this case. The district court uncritically accepted Celgene's arguments, while mysteriously criticizing what it called Plaintiffs' "after-the-fact assertion that what was said to dissuade the Examiner from yet another rejection was nothing more than inconsequential rhetoric." A16. But Plaintiffs made no such assertion, and it is the district court (not Plaintiffs) whose conclusions render the inventors' statements "inconsequential." As shown above, no statements made by the inventors during the prosecution of the '493 patent disavowed any claim scope related to the purity of the taxane—much less clearly and unmistakably so, as settled law requires.

CONCLUSION

For these reasons, the Court should reverse the district court's constructions of the four claim terms here at issue, and vacate the judgment of non-infringement.

Dated: July 7, 2014

Respectfully submitted,

/s/ George C. Lombardi

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ADDENDUM

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UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 11-12226-RGS

CEPHALON, INC. and ACUSPHERE, INC.

v.

CELGENE CORP. and ABRAXIS BIOSCIENCE, LLC

MEMORANDUM AND ORDER ON CLAIM CONSTRUCTION

December 3, 2013

STEARNS, D.J.

Acusphere, Inc., and its exclusive licensee Cephalon, Inc. (collectively, Acusphere), brought this lawsuit against Celgene Corp. and Abraxis BioScience, LLC (collectively, Celgene),[1] alleging that Celgene's antitumor drug Abraxane infringes U.S. Patent RE40, 493, "Porous Paclitaxel Matrices and Methods of Manufacture Thereof" (the '493 patent). To resolve the dispute over the reach of the '493 patent, the parties ask the court to construe the meaning of eleven of the patent's asserted claims. A hearing on the joint request was held on August 28, 2013.

BACKGROUND

[1] Acusphere's Complaint also named Abraxis BioScience, Inc. as a defendant in the suit. The parties subsequently stipulated to the dismissal of Abraxis based on Celgene's representation that Abraxis is merely a holding company that does not manufacture, market, sell, distribute, or profit from Abraxane.

The '493 patent teaches a pharmaceutical composition of paclitaxel that dissolves more than a thousand times faster than non-formulated paclitaxel. Paclitaxel is a taxane compound extracted from the bark of the Pacific yew tree. Taxanes are chemotherapeutic agents that slow the spread of tumor cells in the body by inhibiting cell division. Taxanes, however, are nearly indissoluble in water, making dosages difficult to administer without causing extreme discomfort. The prior formulation of paclitaxel required several hours to infuse and contained Cremophor – a solubizing agent that can cause severe allergic reactions. The '493 patent teaches a remedy for insolubility by integrating paclitaxel (or another taxane) into a dry, porous matrix containing pharmaceutical excipients. Immersed in water, the matrix releases nanoparticles and microparticles of paclitaxel. These particles, in turn, exhibit increased aqueous solubility and dissolve rapidly when diluted in a parenteral fluid medium prior to intravenous injection.

CLAIM CONSTRUCTION

Legal Standards

Claim construction is a question of law for the court's determination. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 970-971 (Fed. Cir. 1995) (en banc). In performing the required analysis, the court first looks to the language of the claims themselves. "It is a bedrock principle of patent law

that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotation marks and citation omitted). A claim term is to be construed in accordance with its "ordinary and customary meaning," which is the "meaning that the term would have to a person of ordinary skill in the art [PHOSITA] in question at the time of the invention, i.e. as of the effective filing date of the patent application." *Id.* at 1312. The ordinary and customary meaning of a claim term is determined "in the context of the entire patent, including the specification." *Id.* at 1313.

Because the purpose of the specification is to teach one skilled in the art the process for replicating the invention, the specification will, in most cases, be "'dispositive; it is the single best guide to the meaning of a disputed term.'" *Id.* at 1315, quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "[T]he specification may reveal a special definition given to a claim term by a patentee that differs from the meaning it would otherwise possess." *Id.* at 1316. However, "the written description in such a case must clearly redefine a claim term so as to put a reasonable competitor or one reasonably skilled in the art on notice that the patentee intended to so redefine that claim term." *Elekta Instrument S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302, 1307 (Fed. Cir. 2000) (internal quotations and citation omitted).

"Absent an express intent to impart a novel meaning, claim terms take on their ordinary meaning." *Id*.

The final element of intrinsic evidence to which a court may turn for guidance is the prosecution history of the patent. While it may not be as reliable as the specification, the prosecution history "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Phillips*, 415 F.3d at 1317. "Where an applicant argues that a claim possesses a feature that the prior art does not possess in order to overcome a prior art rejection, the argument may serve to narrow the scope of otherwise broad claim language." *Seachange Int'l, Inc. v. C-COR Inc.*, 413 F.3d 1361, 1372-1373 (Fed. Cir. 2005).

Disputed Terms

The disputed terms are part of all asserted claims. Independent Claim 1 of the '493 patent is representative.

> A pharmaceutical composition comprising a porous matrix formed of a hydrophilic excipient, a wetting agent and nanoparticles and microparticles of a taxane, wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5μm and a total surface area greater than about 0.5m²/mL, wherein the porous matrix is in a dry powder form, and wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane

nanoparticles and microparticles, wherein the dissolution rate of the taxane nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed taxane.

A. "Nanoparticles" and "Microparticles"

All of the asserted claims require a matrix formed of, *inter alia*, "nanoparticles and microparticles of taxane . . . hav[ing] a mean diameter between about 0.01 and 5µm . . . ." Acusphere argues that because there are no universally accepted size ranges distinguishing nanoparticles from microparticles, it acted as its own lexicographer for purposes of the '493 patent in assigning the particles an undifferentiated diameteric range. Celgene responds that for a PHOSITA, the terms refer to two distinct types of particles, differentiated from one another by size, with nanoparticles being the smaller of the two. Celgene argues that in ordinary usage, nanoparticles are understood to have a diameter between 1 and 1,000 nanometers (nm),while microparticles have a diameter between 1 to 1,000 microns (µm). Morever, according to Celgene, Acusphere's lexicographic argument conflates the diameters of particles in a composition with the *mean* diameter of the population, which renders any distinction between nanoparticles and microparticles in the claims meaningless. As Celgene sees it, "a mean diameter value does not inform a PHOSITA about the size of any particle in a composition, and therefore cannot define whether a composition contains

nanoparticles, microparticles, or both." Def.'s Reply Br. at 1-2. Stated another way, if "nanoparticles *and* microparticles" are defined indistinguishably by their mean diameter, the population could theoretically be comprised entirely of nanoparticles *or* microparticles, contrary to the conjunctive language of the claim.

Finally, Celgene argues that the prosecution history contradicts Acusphere's proposed construction. Claim 1 of what is now the '493 patent originally described the porous matrix as formed of "microparticles of a taxane," with no mention of nanoparticles. The Examiner rejected the claim as obvious based principally on the Desai and Hanes prior art. The Examiner wrote that "a composition and methods for making such, containing paclitaxel and a surfactant, *in micron size* and with a reduced surface area would have been known to one with ordinary skill in the art." Office Action, Nov. 28, 2001, at 4 (emphasis added). In response to this rejection, Acusphere substituted "nanoparticles and microparticles" in place of "microparticles" in the claims, without altering the size range of the particles (0.01 to 5μm), arguing that the Hanes patent disclosed compositions containing microparticles, but not nanoparticles. PTO Corr., Feb. 22, 2002, at 6.

The Examiner again rejected the claims, writing that although Acusphere "asserts that Hanes does not teach the use of nanoparticles in his formulation

. . . it is the examiner's understanding that nanoparticles is merely the size of a particle, and whereas Hanes does not explicitly state the use of nanoparticles, Hanes does teach using particles the same size as the instant invention (5μm)." Office Action, June 3, 2002, at 3. Again responding, Acusphere argued that Desai teaches compositions of nanoparticles and Hanes compositions of particles greater than 5μm. PTO Corr., Aug. 7, 2002, at 5. In distinguishing the '493 patent from the prior art, Acusphere wrote that

> [t]he combination of Desai and Hanes would not lead one skilled in the art to form a porous matrix which dissolves immediately upon exposure to an aqueous medium to release nanoparticles and microparticles of a taxane that have a high surface area and dissolve rapidly. Rather, the combination would lead one to design a formulation where the matrix dissolved rapidly to yield a colloidal solution of taxane. None of the art teaches making a taxane with a faster dissolution rate. None of the art teaches that the available surface area of the taxane should be increased so that the dissolution rate of the taxane rather than the matrix should be increased.

Id. at 5 (emphasis deleted).

While there is no universally agreed definition of the size of a nanoparticle (some sources place the upper range as low as 100nm), the better evidence is that Acusphere's '493 patent in fact relies on the widely accepted definition propounded by Celgene. Telling in this regard is a 1996 textbook co-authored by Howard Bernstein, one of the named inventors on the '493 patent, which states that "[t]he size range covered by microparticles is, according to

definition, between 1 and 1000μm," while nanoparticles range from "1 to 1000nm." *Microparticulate Systems for the Delivery of Proteins and Vaccines* (Smadar Cohen and Howard Bernstein eds., 1996) at 62. Even more telling is the fact that other Acusphere patents in the same field, many credited to the inventors of the '493 patent, incorporate the definition taught by Cohen & Bernstein.

It is true, as Acusphere reminds us, that an inventor is entitled to deference when it acts as its own lexicographer. *See CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366-1367 (Fed. Cir. 2002) (the heavy presumption in favor of ordinary meaning can be overcome when the patentee-lexicographer clearly sets forth a definition of the disputed claim term in either the specification or the file history). Here, however, there is very little evidence in the disputed patent or its history to suggest that Acusphere left a Websterian imprint on the '493 patent. While the '493 patent defines other terms in a definitional format (consistent with Acusphere's practice in other of its patents), it does not formally define nanoparticles or microparticles. While the definition of a patent claim term may be drawn by implication from the specification, to rely successfully on this canon, the patentee must use the disputed term "throughout the entire patent specification, in a manner consistent with only a single meaning . . . ." *Bell Atl. Network Servs., Inc. v.*

Covad Commc'ns Grp., Inc., 267 F.3d 1258, 1271 (Fed Cir. 2001) (citation omitted). But, the only sentence that Acusphere can point to in the specification as supporting a definition by inference, does not even mention nanoparticles. *See* '493 patent col.1 ll.66-67, col.2 ll.1-5 ("Paclitaxel is provided in a porous matrix form which forms nanoparticles and microparticles of paclitaxel when the matrix is contacted with an aqueous medium. The porous matrix with paclitaxel yields upon contact with an aqueous medium *microparticles having a mean diameter between about 0.01 and 5µm* . . . .") (emphasis added).[2]

Acusphere's proposed construction is difficult to square with the claims language of the patent. Claim 1 requires that the matrix be "formed of . . . nanoparticles and microparticles of a taxane, wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5µm and a total surface area greater than about $0.5m^2/mL$ . . . ." If Acusphere intended to define "nanoparticles and microparticles" by the mean diameter of the

[2] Acusphere also argues that Claim 6, which refers to "the mean diameter of the taxane microparticles" as being "between about 0.50 and 5µm," defeats Celgene's proposed construction because it is impossible to have a population of microparticles that are each larger than 1µm in diameter and yet collectively exhibit a mean diameter as low as .50µm. Any inconsistency, however, is a product of Acusphere's at times seemingly random omission of the term "nanoparticles" in the patent.

particles, the separate limitation "wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5μm" would be superfluous. Moreover, if the court were to adopt Acusphere's construction, a natural reading of the claim would transform the surface area requirement ("greater than about 0.5m²/mL") from a separate limitation into a component of the definition of the particles. Acusphere offers no explanation as to why its construction of nanoparticles and microparticles does not also include the specified surface area, nor does it offer any evidence that surface area has ever been used to define the terms.

Finally, the prosecution history provides convincing evidence that Acusphere limited the scope of the '493 patent by distinguishing nanoparticles and microparticles by their size. After an initial rejection by the Examiner based in part on the "micron size" of the particles disclosed in the patent, Acusphere added nanoparticles to the claims and distinguished the claimed invention from the prior art by asserting that Hanes' compositions did not include nanoparticles. Although the Examiner appears to have rejected Acusphere's traversal because of the upper range (5μm) of the particles disclosed in the '493 composition, it is clear from the prosecution history that Acusphere's position before the PTO was that the formulations of the '493 patent included two separate types of particles, characterized by their size. *See*

Andersen Corp. v. Fiber Composites, LLC, 474 F.3d 1361, 1374 (Fed. Cir. 2007) ("We have made clear that an applicant's argument that a prior art reference is distinguishable on a particular ground can serve as a disclaimer of claim scope even if the applicant distinguishes the reference on other grounds as well.") (alterations deleted).

For the above reasons, Celgene's construction will be adopted. *See Texas Digital Sys., Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1202 (Fed. Cir. 2002) ("[U]nless compelled otherwise, a court will give a claim term the *full range of its ordinary meaning* as understood by persons skilled in the relevant art.") (emphasis added).

B. "Nanoparticles and Microparticles *of a taxane*"

The parties next dispute whether the claim term "of a taxane" requires that the particles be composed *only* of a taxane drug. Claim 1 reads in relevant part: "A pharmaceutical composition comprising a porous matrix formed of a hydrophilic excipient, a wetting agent and nanoparticles and microparticles of a taxane . . . ." Acusphere argues that because the claim uses the term "comprising," the composition includes, but is not limited to, taxane particles. *See, e.g., Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l, Inc.*, 246 F.3d 1336, 1348 (Fed. Cir. 2001). The term "comprising" as used in patent law is an open-ended transitional term, and as utilized in the '493 patent,

appears intended to accommodate additional unspecified components of the claimed "pharmaceutical composition." *See Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1271 (Fed. Cir. 1986) (the term "comprising" means "all of the preceding and more"). The term by its positioning in the claim, however, does not operate to unzip the phrase "nanoparticles and microparticles of a taxane" because the claim does not specify "nanoparticles and microparticles *comprising a* taxane." *See Tivo, Inc. v. Echostar Commc'ns Corp.*, 516 F.3d 1290, 1304 (Fed. Cir. 2009) ("[A]lthough the open ended term 'comprising' is used to refer generally to the limitations of the hardware claims, the 'assembles' limitation itself does not contain that term.").

As a fallback, Acusphere points to the structure of the matrix in which the taxane particles are suspended. In addition to the particles, the matrix is composed of hydrophilic excipients and wetting agents, some of which, according to the specification, are not water soluble. The specification also provides that "[u]pon contact with an aqueous medium, water penetrates through the highly porous matrix to dissolve *the water soluble excipients* in the matrix." '493 patent col.3 ll.54-57 (emphasis added). From this, Acusphere argues that "one skilled in the art would know that the microparticles and nanoparticles of a taxane that remain when the matrix dissolves would not only be comprised of the drug, but would include other components, like excipients,

associated with them as well." Pl.'s Br. at 17. Acusphere also points out that neither the claims nor the specification require a "purification step or purity measurement after dissolution of the matrix." Pl.'s Reply Br. at 9. Moreover, "the method and equipment used in the file history to measure particle size cannot distinguish between particles of pure taxane and particles associated with other components of the paclitaxel matrix"; thus, Acusphere contends "it is illogical to conclude that the patent would require that the claimed particles be pure taxane." *Id*.

Celgene responds that it is beside the point that the matrix may be formed of components in addition to the taxane particles, because as Celgene reads the patent, "the specification always and consistently describes the active ingredient, i.e., the nanoparticles and microparticles of a taxane (such as paclitaxel), as being separate and distinct from excipients that form the matrix, and describes the nanoparticles and microparticles of a taxane as being left or remaining after the excipients (including the hydrophilic excipient and wetting agent) that form the matrix dissolve upon exposure to an aqueous medium . . . ." Def.'s Br. at 20; *see, e.g.*, '493 patent col.3 ll.54-58 ("Upon contact with an aqueous medium, water penetrates through the highly porous matrix to dissolve the water soluble excipients in the matrix. A suspension of paclitaxel particles in the aqueous medium remains."); '493 patent col.1 ll.66-67, col.2 l.1

("Paclitaxel is provided in a porous matrix form which forms nanoparticles and microparticles of paclitaxel when the matrix is contacted with an aqueous medium.").

Celgene also cites the prosecution history in support of its proposed construction. After an initial rejection based on the prior art, Acusphere amended claims 1 and 17 to add, among other elements, the limitation that "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles." PTO Corr., Feb. 22, 2002 at 2, 4. In the course of amending the claims, Acusphere distinguished the prior art as follows.

> Hanes discloses a formulation that has two embodiments, one formed of a biodegradable hydrophic, non-water soluble polymer encapsulating drug, which can include a surfactant . . . and the other just of drug and surfactant . . . Desai discloses controlled release, polymer encapsulated formulations. Desai teaches away from anything that would dissolve almost immediately upon administration, to release drug in particulate form.

Id. at 6.

In describing the claimed composition to the PTO, Acusphere wrote, "[t]he matrix is rapidly dissolved upon contact with an aqueous solution, yielding nanoparticles and microparticles of the taxane, *no longer associated with the matrix*. The nanoparticles and microparticles of the taxane lead to an increase[d] rate of dissolution of the taxane." *Id*. at 6 (emphasis added).

Celgene argues that the plain meaning of this description is that Acusphere "relinquished any construction that would permit the nanoparticles and microparticles of a taxane to be formed of the other components that form the matrix, i.e., the hydrophilic excipient or the wetting agent, in addition to the taxane drug." Def.'s Br. at 23. "In particular, the applicants made explicit that the claimed nanoparticles and microparticles of a taxane did not encompass controlled release, polymer encapsulated particles containing paclitaxel and albumin, such as was taught in the prior art." *Id.*

After a second rejection, Acusphere responded that "[t]he combination of Desai and Hanes would not lead one skilled in the art to form a porous matrix which dissolves immediately upon exposure to an aqueous medium to release *nanoparticles and microparticles of a taxane that have a high surface area and dissolve rapidly*." PTO Corr., Aug. 7, 2002, at 5 (emphasis added). According to Celgene, a PHOSITA would understand this statement to mean that taxane is on the surface of the claimed "nanoparticles and microparticles of a taxane," and that the particles' surfaces are free of any additional material or ingredient – such as a polymer of albumin – that would otherwise encapsulate the drug.

Acusphere attempts to distance itself from the prosecution history by arguing that its characterizations of the prior art were mere descriptions, and

should not be viewed as attempts to draw distinctions with Desai and Hanes profound enough to serve as limitations on the claims. As Acusphere phrases it: "[W]hen the Applicants sought to distinguish Desai and Hanes, it was on the basis of the nanoparticles and microparticles themselves dissolving and not whether or not other excipients were associated with those particles." Pl.'s Reply Br. at 10; *see* PTO Corr., Aug. 7, 2002. Acusphere also objects to Celgene's reading of its statement to the Examiner that upon dissolution of the matrix, the taxane particles are "no longer associated with the matrix." According to Acusphere, the inventors were simply describing the "system of the matrix changing state," and did not mean to imply that every non-taxane component of the matrix had to dissolve to leave pure taxane. Pl.'s Reply Br. at 9.

When the plain language of the claim is read in the context of the prosecution history and particularly the effort to escape the teachings of Desai and Hanes, Acusphere's after-the-fact assertion that what was said to dissuade the Examiner from yet another rejection was nothing more than inconsequential rhetoric, is unconvincing at the least.[3] "All limitations in a

[3] "It is well established that statements made during prosecution are used to interpret the scope and meaning of ambiguous claim terminology." *Schumer v. Lab. Computer Sys., Inc.*, 308 F.3d 1304, 1312-1313 (Fed. Cir. 2002).

claim must be considered meaningful." *Lantech, Inc. v. Kelp Machine Co.*, 32 F.3d 542, 546 (Fed. Cir. 1994). Consequently, the court construes the term "of a taxane" to mean "particles formed of only a taxane drug."

C. "Hydrophilic excipient"

Celegene would construe the term "hydrophilic excipient" to mean "an inert component of a pharmaceutical product that will *dissolve upon contact with an aqueous medium*." In support of this construction, Celgene points to the claim language requiring the matrix to dissolve upon exposure to an aqueous medium so as to leave the nanoparticles and microparticles of taxane. Because the matrix is formed, in part, of a hydrophilic excipient, Celgene argues that it follows logically that the hydrophilic excipient, too, dissolves upon exposure to the aqueous medium.

Acusphere responds that it is the *system* of the matrix that must dissolve, and not the components comprising the matrix. Because the matrix is made up of "at least 1 to 95% of the taxane," and the claims depend on the matrix leaving behind nanoparticles and microparticles of taxane upon dissolution, Acusphere argues that nothing in the claim requires every component of the matrix to dissolve. Acusphere further points out that the specification implies that not every excipient, but only water soluble excipients, will dissolve. *See* '493 patent col.3 ll.54-57 ("Upon contact with an aqueous medium, water

penetrates through the highly porous matrix to dissolve the *water soluble excipients* in the matrix.") (emphasis added).

There is nothing in the intrinsic evidence that alters the ordinary and customary meaning of "hydrophilic."[4] The term is not limited to substances that dissolve in water. Both standard and technical dictionaries support Acusphere's construction.[5] *See* Merriam-Webster's Collegiate Dictionary (10th Edition) (1999) ("of, relating to, or having a strong affinity for water"); Stedman's Medical Dictionary (1995) ("Having an affinity for water; readily absorbing or dissolving in water"); International Union of Pure and Applied Chemistry, "Glossary of Terms Used in Physical Organic Chemistry," Pure & Appl. Chem., Vol. 66, pp. 1077-1184, at 1123 (1994) ("water loving"). Thus, the court construes the term "hydrophilic" to mean "an inert substance in a drug vehicle having an affinity for water."

D. "[A porous matrix] formed of a hydrophilic excipient, a wetting agent and nanoparticles and microparticles of a taxane"

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[4] The parties do not substantively dispute the meaning of the term "excipient."

[5] "[D]ictionaries, encyclopedias and treatises, publicly available at the time the patent is issued, are objective resources that serve as reliable sources of information on the established meanings that would have been attributed to the terms of the claim by those of skill in the art." *Texas Digital Sys., Inc.*, 308 F.3d 1193, 1202 (Fed. Cir. 2002).

Based on the prosecution history, Celgene contends that the matrix must be formed of four separate and distinct components: (1) a hydrophilic excipient, (2) a wetting agent, (3) nanoparticles of a taxane, and (4) microparticles of a taxane. Acusphere initially claimed a porous matrix formed of only a wetting agent and microparticles of a taxane, but added a hydrophilic excipient and nanoparticles of a taxane after an obviousness rejection by the Examiner. It wrote that the Hanes prior art disclosed a surfactant and drug, but "there are no nanoparticles, nor is there a matrix formed of a hydrophilic excipient that dissolves upon contact with water . . . ." PTO Corr., Feb. 22, 2002, at 6. Celgene argues that because a surfactant disclosed in the Hanes patent is also a wetting agent, Acusphere's addition of "hydrophilic excipient" to the claims must mean a substance other than the wetting agent.

No amount of argument, however, can overcome the plain language of the claims and the specification. Dependent claims 45-47 explicitly states that "the hydrophilic excipient is the wetting agent."[6] '493 patent cls.45-47. Moreover, the specification states that "hydrophilic excipients, such as water soluble polymers or sugars . . . can serve . . . as wetting agents . . . ." *Id.* at col.3

[6] Celgene argues that because these claims were added during the reissue process, they impermissibly seek to recapture subject matter surrendered during prosecution and are thus invalid. As discussed above, the prosecution history does not support this argument.

ll.51-54. Although Acusphere wrote that the prior art contained a wetting agent but not a hydrophilic excipient, there is no indication that it intended to include a limitation that the substances be distinct. "[A porous matrix] formed of a hydrophilic excipient, a wetting agent and nanoparticles and microparticles of a taxane," is therefore construed to mean that the porous matrix is formed of at least three components including (1) a hydrophilic excipient, (2) a wetting agent, and (3) nanoparticles and microparticles of a taxane, wherein the hydrophilic excipient and the wetting agent need not be distinct from one another.

E. "Mean diameter" and "wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5µm and a total surface area greater than about 0.5m²/mL, wherein the porous matrix is in a dry powder form"

Celgene first contends that the claim term "mean diameter" is indefinite because nothing in the intrinsic evidence specifies the mean diameter to be calculated or the calculation methodology to be used. *See Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1341 (Fed. Cir. 2003) (finding claims invalid because, depending on the preparation method chosen, "the testing results will necessarily fall within or outside the claim scope"). The prosecution history makes clear, however, that the '493 patent refers to a

volume mean diameter measurement. As discussed earlier in Section A, Acusphere attempted to distinguish the Hanes patent, in part, based on the size of the taxane particles. In his exchanges with Acusphere, the Examiner compared the size of the Hanes particles with those claimed in the '493 patent. The Hanes patent measured particle size by "mass mean diameter," which is a synonym for "volume mean diameter." '913 patent col.7 l.54. Thus, in order to make the particle size comparison with Hanes, the Examiner and Acusphere recognized that the volume mean diameter defined the particle size for the '493 patent as well.

The Hanes patent also disclosed that "the mass mean diameter of the particles can be measured using a Coulter Multisizer II." *Id*. at col. 7 l.55. Acusphere's provisional application (from which the '493 patent derives) states that "[t]otal surface area values can be provided using standard Coulter Counter equipment and techniques." U.S. Provisional Application No. 60/158,659. Acusphere argues persuasively that the prosecution history runs counter to Celgene's claim that the patent does not specify a technique to be used to measure mean diameter. Acusphere also points to the instruction in the '493 patent's specification that the "[t]otal surface area values of the microparticles can be determined using standard particle sizing equipment and techniques." '493 patent col.3 ll.21-23. And, finally, Acusphere maintains that

a PHOSITA would have no difficulty measuring particle size with a reasonable degree of accuracy using any one of a number of standardized techniques.

Celgene next argues that if the claim is not indefinite, it should be construed to mean that the diameter and surface area measurements refer only to nanoparticles and microparticles of taxane, and further, that the measurements are to be made when the matrix is in a dry powder form. Why Celgene is right in the first instance is discussed in Section B. However, the specification makes clear that the measurements are to be made after the matrix comes into contact with an aqueous medium. There it is said that "[t]he porous matrix with paclitaxel *yields upon contact* with an aqueous medium microparticles having a mean diameter between about 0.01 and 5 um and a total surface area greater than about 0.5 m^2/mL." '493 patent col.2 ll.1-5 (emphasis added); *see also id*. at col.3 ll.15-21 ("The matrix *must yield* microparticles of paclitaxel, *upon contact* with an aqueous medium which preferably have a diameter between about 10nm and 5µm, more preferably between about 50nm and 5µm.") (emphasis added). This construction is reinforced by the "m^2/mL" unit of measurement used to describe the surface area of the nanoparticles and microparticles in the claims. If the taxane particles were intended to be measured in powder form, the unit of measurement would be "m^2/g" – the units used in the specification to describe

the results of surface area analysis of the dry porous matrix.[7]

The court will construe the disputed claim term "mean diameter" as a proxy for the term "volume mean diameter." The court sees no need to construe the phrase "wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5μm and a total surface area greater than about 0.5m²/mL, wherein the porous matrix is in a dry powder form." It has a plain and ordinary meaning when read in context with the court's ruling in Section B.

F. "Matrix dissolves" and "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles"

Celgene argues that this claim limitation is indefinite on two grounds. First, it asserts that the claim is "nonsensical" because the patent claims as a whole require that the matrix be formed of nanoparticles and microparticles of a taxane, while also requiring that the matrix dissolve to leave the taxane particles. The court does not see the inconsistency. While the claim language

[7] Celgene also contends that the specification states that the claim phrase "total surface area" means the "sum of internal and external surface area." But the specification refers to the surface area of the dry porous matrix as measured by BET analysis, not the surface area of the nanoparticles and microparticles remaining in suspension after the matrix is dissolved.

and specification repeatedly state that the matrix must dissolve to leave behind taxane particles, nowhere is it said that the dissolving of the matrix is defined "by reference to whether all of the taxane nanoparticles and microparticles dissolve." Def.'s Br. at 38. The specification states that "[u]pon contact with an aqueous medium, water penetrates through the highly porous matrix to dissolve the water soluble excipients in the matrix. *A suspension of paclitaxel particles in the aqueous medium remains*." '493 patent col.3 ll.54-58 (emphasis added). The patent thus contemplates two distinct steps: "(1) dissolution of the porous matrix to leave nanoparticles and microparticles of paclitaxel suspended in the aqueous reconstitution medium; and (2) the subsequent dissolution of the nanoparticles and microparticles of paclitaxel that occurs in a larger volume of aqueous medium or once administered to the patient." Pl.'s Reply Br. at 20. This construction is confirmed by the prosecution history. In distinguishing the '493 patent from Hanes, Acusphere wrote that "[n]one of the art teaches that the available surface area of the taxanes should be increased so that the dissolution rate of the taxane *rather than the matrix* should be increased." PTO Corr., Aug. 7, 2002, at 5 (emphasis in original); *see also id.* at 6 ("Applicants' claimed process *yields taxane that dissolves* at a rate that may be 1000 times shorter than for bulk taxane.") (emphasis added).

Celgene's second argument for indefiniteness is that the claim phrase states only a "functional" limitation and that the patent "fails to provide the qualitative parameters necessary for a PHOSITA to determine whether, for any given composition, the matrix dissolves to leave the taxane nanoparticles and microparticles." Def.'s Reply Br. at 23. "In particular, the claims do not specify the conditions, such as the specific volume or type of aqueous medium, that must be added to satisfy the limitation that the matrix will dissolve but the taxane nanoparticles and microparticles will not . . . ." Def.'s Br. at 39. Acusphere responds that the patent provides that the formulations do not require a particular aqueous medium, but clearly contemplates various embodiments. Pl.'s Reply Br. at 22 (citing the specification statement "an aqueous medium, such as physiological saline" and the T80/PBS solution disclosed in Example 3). Thus, Acusphere contends, "the patent only requires assessing infringement in the given aqueous medium and volume used as the reconstitution medium. If taxane nanoparticles and microparticles are left in the reconstitution medium, the claim limitation is met." *Id*. Because the court agrees with Acusphere on this point, it will construe "matrix dissolves" as conforming to its plain and ordinary meaning.

However, for the reasons discussed in Section B, the court will largely adopt Celegene's proposed interpretation that the hydrophilic excipients and

wetting agents may not attach to the taxane drug. The second part of the disputed claim is therefore construed to mean that the porous matrix must dissolve to leave only taxane drug in the form of nanoparticles and microparticles that are no longer associated with either the hydrophilic excipient or the wetting agent.

G. "Solution" and "wherein the dissolution rate of the taxane nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed taxane"

Celgene also contends that this claim phrase is indefinite because, as discussed above in Section F, "dissolution rate is concentration dependent, and the claims do not specify the particular concentrations at which this claim limitation must be met." Def's Br. at 44. Acusphere responds that Example 3 of the patent clearly defines the method of determining the dissolution rate of the taxane particles relative to unprocessed taxane and notes that in explaining the new claim limitation, it specifically referred the Examiner to Example 3 and the results associated with the testing in Figure 1. PTO Corr., Aug. 7, 2002, at 3, 6. The court will therefore adopt Acusphere's construction of the phrase "wherein the dissolution rate of the taxane nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed

taxane" to include "as measured according to Example 3 of the '493 patent."[8] Finally,"solution" is a word of ordinary meaning that is given no special definition in the '493 patent. Consequently, the court will adopt Celgene's construction: "a homogenous mixture of two or more substances."

ORDER

The disputed claim terms will be construed for all further purposes in this litigation as the court has indicated in the body of this opinion.

SO ORDERED.

/s/ Richard G. Stearns

_____

UNITED STATES DISTRICT JUDGE

[8] Celgene argues that, if Acusphere's construction is adopted, it should be further construed to exclude formulations in which after exposure to an aqueous medium, particles of paclitaxel and albumin can remain stable in a suspension for at least 3 days at a concentration between 1.2 to 3mg/ml. This interpretation is based on Acusphere's statement to the Examiner that "Desai teaches that the dry particles reconstituted in aqueous solutions (col. 6, lines 10-17) are stable for at least three days (*see* col. 12, lines 33-40). Not only do Desai's taxane particles not dissolve upon contact with water, but it is critical to have them remain as a suspension in order to achieve the desired tissue distribution and concentration (col. 6, lines 46-56)." PTO Corr., Aug. 7, 2002, at 6. It is unclear how this description of the dissolution of the matrix and the stability of the remaining taxane particles relates to the dissolution rate of the taxane particles themselves.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

CEPHALON, INC. and ACUSPHERE, INC., Plaintiffs, v. **CELGENE CORP. and ABRAXIS BIOSCIENCE, LLC,** Defendants.	Civil Action No.: 1:11-cv-12226-RGS

STIPULATED FINAL JUDGMENT OF NONINFRINGEMENT

WHEREAS Plaintiffs Cephalon, Inc. and Acusphere, Inc. (collectively, "Plaintiffs") commenced this patent infringement action on December 14, 2011, accusing Defendants Celgene Corp. and Abraxis Bioscience LLC (collectively, "Defendants") of infringing certain claims, including Claim 1, of U.S. Patent No. RE40,493 ("the '493 patent");

WHEREAS Defendants filed an Answer denying Plaintiffs' claims and asserting counterclaims for declaratory judgment of noninfringement of the '493 patent and declaratory judgment of invalidity of the '493 patent;

WHEREAS on December 3, 2013, this Court issued a Claim Construction Order, wherein, as a matter of law, it rejected Celgene's indefiniteness arguments respecting certain claim terms and construed those claim terms and others in the '493 patent (Dkt. 75);

WHEREAS in the Claim Construction Order the Court construed, *inter alia*, the following terms as having the following meanings:

- "nanoparticles" are "particles that have a diameter of between about 1 to 1000 nanometers and less than that of microparticles";

- "microparticles" are "particles that have a diameter of between about 1 to 1000 microns and greater than that of nanoparticles";
- "nanoparticles and microparticles of a taxane" are "particles formed of only a taxane drug"; and
- "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles" means that when the matrix is exposed to an aqueous medium, "the porous matrix must dissolve to leave only taxane drug in the form of nanoparticles and microparticles that are no longer associated with either the hydrophilic excipient or the wetting agent";

WHEREAS, while each party reserves its right to appeal, Plaintiffs stipulate that under the Court's constructions of any one of the terms "nanoparticles," "microparticles" "nanoparticles and microparticles of a taxane", or "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles" Plaintiffs cannot sustain their burden of proving infringement of the '493 patent by the accused product; and

WHEREAS, so that a final judgment may be entered, Defendants stipulate to dismissal of their counterclaims without prejudice.

NOW THEREFORE, IT IS HEREBY ORDERED AND ADJUDGED THAT:

1. The accused product does not infringe any valid claim of the '493 patent under the constructions of "nanoparticles," "microparticles," "nanoparticles and microparticles of a taxane," or "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles" rendered by this Court;

2. Accordingly, without prejudice to any party's right to appeal, the parties hereby stipulate:

a. to a judgment of non-infringement with prejudice with respect to all Counts of Plaintiffs' Complaint in favor of all Defendants and against Plaintiffs, and

b. to dismissal of Defendants' counterclaims without prejudice, which counterclaims may be reasserted without leave of Court in the event this Judgment or the Court's Claim Construction Order is reversed or vacated in whole or in part and the case is remanded to this Court for future proceedings;

3. This Judgment, once entered, fully and finally disposes of all claims and counterclaims asserted in this matter, and in the event of an appeal from any portion hereof, the prevailing party shall be entitled to defend this Judgment on any ground presented to this Court; and

4. The parties hereby stipulate and agree, with the concurrence of the Court, that consideration of the issues of the taxation of costs and the entitlement of fees, if any, pursuant to 35 U.S.C. § 285 or on any other basis, shall be deferred in the event there is an appeal of this stipulated final judgment until after the conclusion of such appeal.

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Respectfully submitted this 18th day of March, 2014,

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SO ORDERED.

Dated: March 18, 2014

Richard G. Stearns
Hon. Richard G. Stearns
United States District Judge

US00RE40493E

(19) **United States**
(12) **Reissued Patent**
Straub et al.

(10) **Patent Number: US RE40,493 E**
(45) **Date of Reissued Patent: *Sep. 9, 2008**

(54) **POROUS PACLITAXEL MATRICES AND METHODS OF MANUFACTURE THEREOF**

(75) Inventors: **Julie A. Straub**, Winchester, MA (US); **Howard Bernstein**, Cambridge, MA (US); **Donald E. Chickering, III**, Framingham, MA (US); **Sarwat Khattak**, Hadley, MA (US); **Greg Randall**, Arlington, MA (US)

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(*) Notice: This patent is subject to a terminal disclaimer.

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(22) Filed: **Aug. 26, 2005**

Related U.S. Patent Documents

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Appl. No.: **09/798,824**
Filed: **Mar. 2, 2001**

U.S. Applications:
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(60) Provisional application No. 60/186,310, filed on Mar. 2, 2000, provisional application No. 60/158,659, filed on Oct. 8, 1999, and provisional application No. 60/136,323, filed on May 27, 1999.

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A61K 9/14 (2006.01)
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(58) **Field of Classification Search** 424/489, 424/484, 422, 426; 514/951, 449; 549/512
See application file for complete search history.

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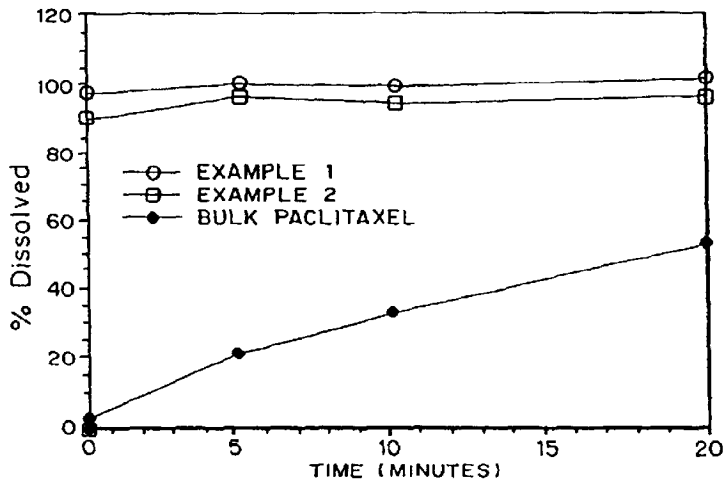
(57) **ABSTRACT**

Paclitaxel is provided in a porous matrix form, which allows the drug to be formulated without Cremophor and administered as a bolus. The paclitaxel matrices preferably are made using a process that includes (i) dissolving paclitaxel in a volatile solvent to form a paclitaxel solution, (ii) combining at least one pore forming agent with the paclitaxel solution to form an emulsion, suspension, or second solution, and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of paclitaxel. The pore forming agent can be either a volatile liquid that is immiscible with the paclitaxel solvent or a volatile solid compound, preferably a volatile salt. In a preferred embodiment, spray drying is used to remove the solvents and the pore forming agent. In a preferred embodiment, microparticles of the porous paclitaxel matrix are reconstituted with an aqueous medium and administered parenterally, or processed using standard techniques into tablets or capsules for oral administration.

47 Claims, 1 Drawing Sheet



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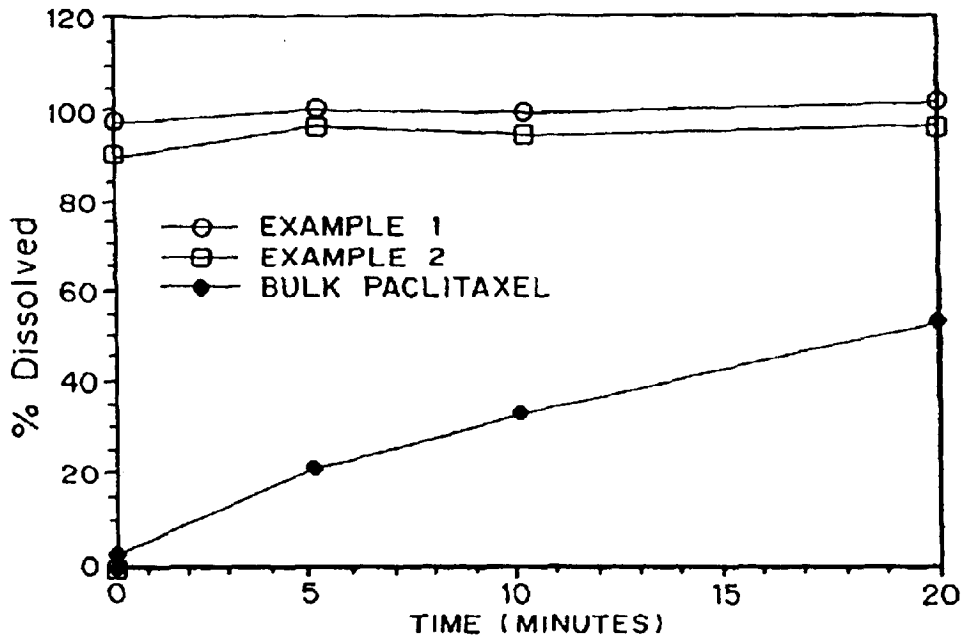
120
100
80
60
40
20
0
% Dissolved
EXAMPLE 1
EXAMPLE 2
BULK PACLITAXEL
0
5
10
15
20
TIME (MINUTES)

FIG. 1

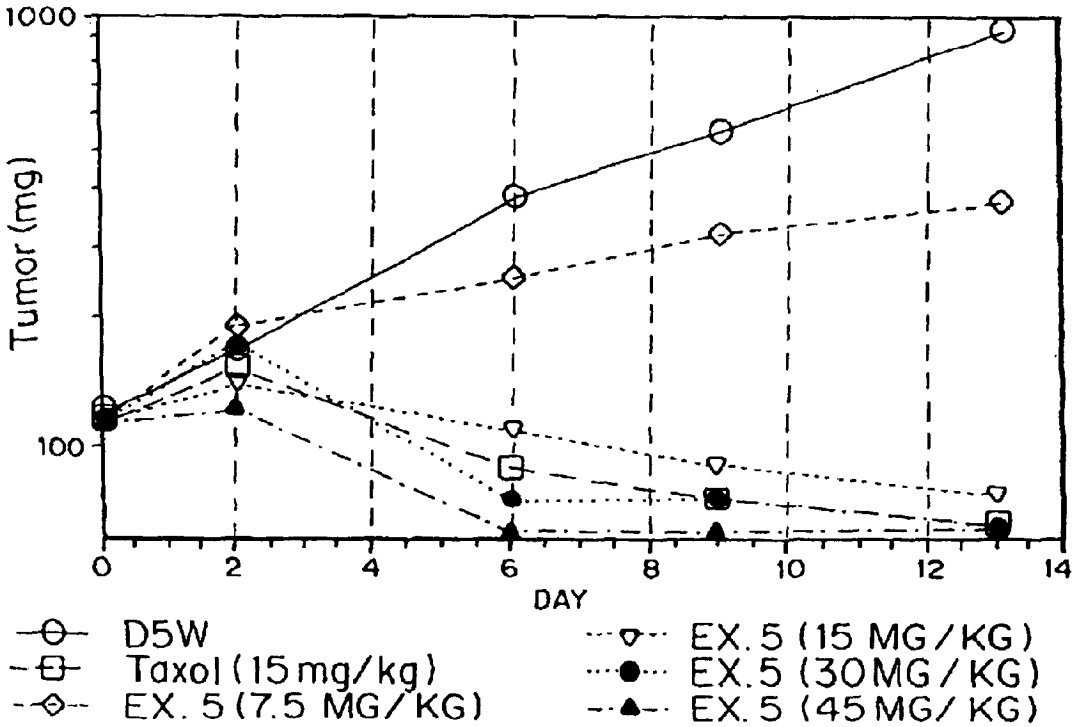
1000
100
Tumor (mg)
0
2
4
6
8
10
12
14
DAY
D5W
Taxol (15 mg/kg)
EX. 5 (7.5 MG/KG)
EX. 5 (15 MG/KG)
EX. 5 (30 MG/KG)
EX. 5 (45 MG/KG)

FIG. 2

POROUS PACLITAXEL MATRICES AND METHODS OF MANUFACTURE THEREOF

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This invention claims priority U.S. Ser. No. 60/186,310 filed Mar. 2, 2000, and is a continuation to PCT/US00/14578 filed May 25, 2000, which claims priority to U.S. Ser. No. 60/136,323 filed May 27, 1999, and U.S. Ser. No. 60/158,659 filed Oct. 8, 1999.

BACKGROUND OF THE INVENTION

This invention generally relates to formulations of paclitaxel and more particularly to methods of making formulations of paclitaxel.

Paclitaxel is a natural product which has been shown to possess cytotoxic and antitumor activity. Indeed, paclitaxel may be among the most active single agent for ovarian and breast cancers. This compound is found in small concentrations in the Taxus brevifolia species such as the Pacific yew tree among other Taxus species. While having an unambiguous reputation of tremendous therapeutic potential, paclitaxel as a therapeutic agent has some patient related drawbacks. These stem, in part, from its extremely low solubility in water, which makes it difficult to provide in suitable dosage form. Because of paclitaxel's poor aqueous solubility, the current approved clinical formulation consists of a 6 mg/ml solution of paclitaxel in 50% polyoxyethylated castor oil (CREMOPHOR EL™) and 50% dehydrated alcohol. Am. J. Hosp. Pharm. 48:1520-24 (1991). In some instances, severe reactions, including hypersensitivity, occur in conjunction with the CREMOPHOR™ administered in conjunction with paclitaxel to compensate for its low water solubility. As a result of the incidence of hypersensitivity reactions to the commercial paclitaxel formulations and the potential for paclitaxel precipitation in the blood, the formulation must be infused over several hours. In addition, patients must be pretreated with steroids and antihistamines prior to the infusion.

In response to the hypersensitivity related to the CREMOPHOR™, the increasing recognition of paclitaxel's promise as an antineoplastic, and the undesirability of having to infuse the paclitaxel over several hours, there remains a need to develop improved formulations of the paclitaxel which can be administered as bolus injections.

It is therefore an object of the present invention to provide compositions of the paclitaxel without the solubilizing agent, CREMOPHOR™ which is present in the commercial formulation.

It is another object of the present invention to provide methods for producing the porous dry powder formulations of paclitaxel or docetaxol.

It is another object of the present invention to provide compositions providing enhanced dissolution of paclitaxel or docetaxol in a formulation suitable for administration by a variety of routes, including, but not limited to, parenteral, mucosal, oral, and topical administration, for local, regional, or systemic effect.

It is further object of the present invention to provide paclitaxel compositions for administration as a bolus injection instead of by infusion.

SUMMARY OF THE INVENTION

Paclitaxel is provided in a porous matrix form which forms nanoparticles and microparticles of paclitaxel when

the matrix is contacted with an aqueous medium. The porous matrix with paclitaxel yields upon contact with an aqueous medium microparticles having a mean diameter between about 0.01 and 5 μm and a total surface area greater than about 0.5 m^2/mL. The dry porous matrix is in a dry powder form having a TAP density less than or equal to 1.0 g/mL.

The porous matrices that contain the paclitaxel are preferably made using a process that includes (i) dissolving a paclitaxel in a volatile solvent to form a paclitaxel solution, (ii) combining at least one pore forming agent with the paclitaxel solution to form an emulsion, suspension, or second solution, and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the dry porous matrix of paclitaxel. The resulting porous matrix has a faster rate of dissolution following administration to a patient, as compared to non-porous matrix forms of the paclitaxel. The pore forming agent can be either a volatile liquid that is immiscible with the paclitaxel solvent or a volatile solid compound, preferably a volatile salt. If the pore forming agent is a liquid, the agent is emulsified with the paclitaxel solution. If the pore forming agent is a solid, the agent is (i) dissolved in the paclitaxel solution, (ii) dissolved in a solvent that is not miscible in the paclitaxel solvent and then emulsified with the paclitaxel solution, or (iii) suspended as solid particulates in the paclitaxel solution. Optionally, hydrophilic excipients, wetting agents, and/or tonicity agents may be added to the paclitaxel solvent, the pore forming agent solvent, or both. The solution, emulsion, or suspension of the pore forming agent in the paclitaxel solution is then processed to remove the paclitaxel solvent and the pore forming agent, as well as any pore forming agent solvent. In a preferred embodiment, spray drying, optionally followed by lyophilization, fluid bed drying, or vacuum drying, is used to remove the solvents and the pore forming agent.

An advantage of the formulations is that they can be administered as a bolus, when the paclitaxel normally must be infused to avoid toxicity and to avoid precipitation of the drug. By avoiding precipitation of paclitaxel in vivo, the formulations can also be administered intrarterially, intravenously, locally, intracranially, intrathecally, or directly into a tumor. An additional advantage is the formulations can be administered in reduced volumes.

In one embodiment, the matrix further includes a pegylated excipient with the paclitaxel. The pegylated excipient shields the paclitaxel from macrophage uptake, which prolong its half-life or enhance bioavailability of the paclitaxel.

In a preferred embodiment, the porous paclitaxel matrix is reconstituted with an aqueous medium and administered parenterally, such as intramuscularly, subcutaneously, or intravenously. Alternatively, the porous paclitaxel matrix can be further processed using standard techniques into tablets or capsules for oral administration or into rectal suppositories, delivered using a dry powder inhaler for pulmonary administration, or mixed/processed into a cream or ointment for topical administration.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph of the in vitro dissolution rate (percent dissolved versus time) for non-formulated and various formulated paclitaxel in porous matrix form.

FIG. **2** is a graph of median MDA-MB 435 breast tumor weight in female athymic NCr-nu mice following five days of therapy with paclitaxel in porous matrix form.

DETAILED DESCRIPTION OF THE INVENTION

Compositions of paclitaxel without the solubilizing agent, CREMOPHOR™, and which can be administered as a bolus

are disclosed. The compositions are porous dry powders, which upon the addition of an aqueous medium form a suspension of paclitaxel nanoparticles and microparticles. Methods for producing the formulations of paclitaxel include using pore forming agents. The compositions may contain hydrophilic excipients, such as water soluble polymers and sugars, and wetting agents, such as surfactants.

I. Paclitaxel Matrix Compositions

The porous paclitaxel matrix is at least 1 to 95%, preferably at least about 10%, and more preferably between about 10 and 70%, paclitaxel by weight. The matrices also may contain hydrophilic excipients such as water soluble polymers or sugars, wetting agents such as surfactants, and tonicity agents.

The matrix must yield microparticles of paclitaxel, upon contact with an aqueous medium which preferably have a diameter between about 10 nm and 5 μm, more preferably between about 50 nm and 5 μm. The average total surface area of the microparticles contained within the porous matrix, which typically is in the form of a dry powder, is 0.5 m^2/mL or greater. Total surface area values of the microparticles can be determined using standard particle sizing equipment and techniques.

The paclitaxel matrix must be sufficiently porous to yield microparticles, upon contact with an aqueous medium, having these parameters. Measurements useful in characterizing the porosity of the paclitaxel matrix are the bulk density or the transaxial pressure ("TAP") density of the dry porous matrix (dry powder) and the total surface area (sum of internal and external surface area) of the dry porous matrix. The TAP density preferably is less than about 1.0 g/ml, more preferably less than 0.8 g/ml. This level of porosity of the matrix, characterized by density, provides sufficient surface area to enhance wetting of the dry porous matrix and enhance paclitaxel dissolution.

The total surface area (sum of internal and external surface area) of the porous matrix can be measured, for example, by BET surface area analysis. In some embodiments, the total surface area of the porous matrix preferably is greater than 0.1 m^2/g, more preferably greater than or equal to 0.2 m^2/g. This level of total surface area provides sufficient surface area to enhance wetting of the dry porous matrix and enhance drug dissolution.

1. Paclitaxel

As generally used in the description herein, "paclitaxel" includes taxanes and derivatives thereof, including paclitaxel and docetaxel, which have anticancer or antiangiogenic activity. Paclitaxel was specifically used in the examples which follow.

2. Excipients

The matrices may contain hydrophilic excipients, such as water soluble polymers or sugars, which can serve as bulking agents or as wetting agents, wetting agents such as surfactants or sugars, and tonicity agents. Upon contact with an aqueous medium, water penetrates through the highly porous matrix to dissolve the water soluble excipients in the matrix. A suspension of paclitaxel particles in the aqueous medium remains. The total surface area of the resultant low aqueous solubility paclitaxel microparticles is increased relative to the unprocessed paclitaxel and the dissolution rate of the paclitaxel is increased.

One of skill in the art can select appropriate excipients for use in the paclitaxel matrix compositions, considering a variety of factors, such as the paclitaxel to be administered, the route of administration, the dosage, and the preferred dissolution rate. For example, the excipients can function as bulking agents, release-modifiers, wetting agents, tonicity

agents, or combinations thereof. Preferred excipients include hydrophilic polymers, wetting agents, and sugars. The amount of excipient in the paclitaxel matrix is less than about 95%, more preferably less than about 80%, by weight of the paclitaxel matrix.

The hydrophilic excipients, wetting agents, and tonicity agents may be added to the paclitaxel solution, the pore forming agent, or both, during production of the matrix.

(i) Hydrophilic Polymers

The polymers that can be used in the paclitaxel matrices described herein include both synthetic and natural polymers, either non-biodegradable or biodegradable. Representative synthetic polymers include polyethylene glycol ("PEG"), polyvinyl pyrrolidone, polymethacrylates, polylysine, poloxamers, polyvinyl alcohol, polyacrylic acid, polyethylene oxide, and polyethyoxazoline. Representative natural polymers include albumin, alginate, gelatin, acacia, chitosan, cellulose dextran, ficoll, starch, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxy-propylmethyl cellulose, hyaluronic acid, carboxyethyl cellulose, carboxymethyl cellulose, deacetylated chitosan, dextran sulfate, and derivatives thereof. Preferred hydrophilic polymers include PEG, polyvinyl pyrrolidone, poloxamers, hydroxypropyl cellulose, and hydroxyethyl cellulose.

The hydrophilic polymer selected for use in a particular paclitaxel matrix formulation is based on a variety of factors, such as the polymer molecular weight, polymer hydrophilicity, and polymer inherent viscosity. The hydrophilic polymer can be used as a bulking agent or as a wetting agent.

(ii) Sugars

Representative sugars that can be used in the paclitaxel matrices include mannitol, sorbitol, xylitol, glucitol, ducitol, inositiol, arabinitol, arabitol, galactitol, iditol, allitol, fructose, sorbose, glucose, xylose, trehalose, allose, dextrose, altrose, gulose, idose, galactose, talose, ribose, arabinose, xylose, lyxose, sucrose, maltose, lactose, lactulose, fucose, rhamnose, melezitose, maltotriose, and raffinose. Preferred sugars include mannitol, lactose, sucrose, sorbitol, trehalose, glucose, and are adjusted to provide osmolality if administered parenterally or to provide wetting of the porous paclitaxel matrix or the paclitaxel microparticles within the matrix.

(iii) Wetting Agents

Wetting agents can be used to facilitate water ingress into the matrix and wetting of the paclitaxel particles in order to facilitate dissolution.

Representative examples of wetting agents include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., TWEEN™s), polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxy propylcellulose, hydroxypropylmethylcellulose phthlate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton) is another useful wetting agent. Most of these wetting agents are known pharmaceutical excipients and are described in detail in the Handbook of Pharmaceutical

Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 1986).

Preferred wetting agents include polyvinylpyrrolidone, polyethylene glycol, tyloxapol, poloxamers such as PLURONIC™ F68, F127, and F108, which are block copolymers of ethylene oxide and propylene oxide, and polyxamines such as TETRONIC™ 908 (also known as POLOXAMINE™ 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (available from BASF), dextran, lecithin, dialkylesters of sodium sulfosuccinic acid such as AEROSOL™ OT, which is a dioctyl ester of sodium sulfosuccinic acid (available from American Cyanimid), DUPONOL™ P, which is a sodium lauryl sulfate (available from DuPont), TRITON™ X-200, which is an alkyl aryl polyether sulfonate (available from Rohm and Haas), TWEEN™ 20 (*polysorbate 20*) and TWEEN™ 80 (*polysorbate 80*), which are polyoxyethylene sorbitan fatty acid esters (available from ICI Specialty Chemicals), Carbowax 3550 and 934, which are polyethylene glycols (available from Union Carbide), CRODESTA™, which is a mixture of sucrose stearate and sucrose distearate, and CRODESTA™ SL-40 (both available from Croda Inc.), and SA90HCO, which is $C_{18}H_{37}CH_2(CON(CH_3)CH_2(CHOH)_4 CH_2OH)_2$.

Wetting agents which have been found to be particularly useful include TETRONIC™ CRODESTA™ 908, the TWEENS™, PLURONIC™ F-68 and polyvinylpyrrolidone. Other useful wetting agents include decanoyl-N-methylglucamide; n-decyl-β-D-glucopyranoside; n-decyl-β-D-maltopyranoside; n-dodecyl-β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl-β-D-thioglucoside; n-hexyl-β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl-β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; and octyl-β-D-thioglucopyranoside. Another preferred wetting agent is P-isononylphenoxypoly(glycidol), also known as OLIN™-10G or Surfactant 10-G (commercially available as 10G from Olin Chemicals). Two or more wetting agents can be used in combination.

(iv) Tonicity or Osmolality Agents

The porous paclitaxel matrices may include one or more tonicity agents, such as salts (e.g., as sodium chloride or potassium chloride) or sugars (such as mannitol, dextrose, sucrose, or trehalose) to adjust a hypotonic solution of a paclitaxel to isotonic so that the paclitaxel, when in solution, is physiologically compatible with the cells of the body tissue of the patient. The type and amount of tonicity agent can be selected by one of skill in the art using known techniques.

(v) Pegylated Excipients

In one embodiment, the matrix further includes a pegylated excipient. Such pegylated excipients include, but are not limited to, pegylated phospholipids, pegylated proteins, pegylated peptides, pegylated sugars, pegylated polysaccharides, pegylated block co-polymers with of the blocks being PEG, and pegylated hydrophobic compounds such as pegylated cholesterol. The pegylated excipient beneficially envelops or shields the paclitaxel from macrophage uptake, which prolongs its half-life or enhances bioavailability of the paclitaxel.

Representative examples of pegylated phospholipids include 1,2-diacyl-sn-glycero-3-phosphoethanolamine-N-[Poly(ethyleneglycol) 2000] ("PEG 2000 PE") and 1,2-diacyl-sn-glycero-3-phosphoethanolamine-N-[Poly (ethylene glycol) 5000] ("PEG 5000 PE"), where the acyl group is selected, for example, from dimyristoyl, dipalmitoyl, distearoyl, diolcoyl, and 1-palmitoyl-2-oleoyl.

Other polyalkyleneoxides can be used in place of the polyethylene glycol.

II. Volatile Solvents

The choice of solvent depends on the paclitaxel. In a preferred embodiment, the solvent is an organic solvent that is volatile, has a relatively low boiling point, or can be removed under vacuum, and which is acceptable for administration to humans in trace amounts. Representative solvents include acetic acid, acetaldehyde dimethyl acetal, acetone, acetonitrile, chloroform, chlorofluorocarbons, dichloromethane, dipropyl ethyl, diisopropyl ether, N,N-dimethylformamide (DMF), formamide, demethyl sulfoxide (DMSO), dioxane, ethanol, ethyl acetate, ethyl formate, ethyl vinyl ether, methyl ethyl ketone (MEK), glycerol, heptane, hexane, isopropanol, methanol, isopropanol, butanol, triethylamine, nitromethane, octane, pentane, tetrahydrofuran (THF), toluene, 1,1,1-trichloroethane, 1,1,2-trichloroethylene, water, xylene, and combinations thereof. In general, the paclitaxel is dissolved in the volatile solvent to form a paclitaxel solution having a concentration of between 0.01 and 80% weight to volume (w/v), more preferably between 0.025 and 30% (w/v).

Aqueous solvents or mixtures of aqueous and organic solvents, such as water-alcohol mixtures, can be used to dissolve the drug. In a preferred embodiment the volatile solvent is an aqueous mixture of an alcohol such as methanol or ethanol where the alcohol percent is in the range 40-100% (v/v).

III. Pore Forming Agents

Pore forming agents are volatile materials that preferably are used during the process to create porosity in the resultant matrix. The pore forming agent can be a volatilizable solid or volatilizable liquid.

1. Liquid Pore Forming Agent

The liquid pore forming agent must be immiscible with the paclitaxel solvent and volatilizable under processing conditions compatible with the paclitaxel. To effect pore formation, the pore forming agent first is emulsified with the paclitaxel solvent. Then, the emulsion is further processed to remove the paclitaxel solvent and the pore forming agent simultaneously or sequentially using evaporation, vacuum drying, spray drying, fluid bed drying, lyophilization, or a combination of these techniques.

The selection of liquid pore forming agents will depend on the paclitaxel solvent. Representative liquid pore forming agents include water; dichloromethane; alcohols such as ethanol, methanol, or isopropanol; acetone; ethyl acetate; ethyl formate; dimethylsulfoxide; acetonitrile; toluene; xylene; dimethylforamide; ethers such as THF, diethyl ether, or dioxane; triethylamine; foramide; acetic acid; methyl ethyl ketone; pyridine; hexane; pentane; furan; water; and cyclohexane.

The liquid pore forming agent typically is used in an amount that is between 1 and 50% (v/v), preferably between 5 and 25% (v/v), of the paclitaxel solvent emulsion.

2. Solid Pore Forming Agent

The solid pore forming agent must be volatilizable under processing conditions which do not harm the paclitaxel compositions. The solid pore forming agent can be (i) dissolved in the paclitaxel solution, (ii) dissolved in a solvent which is not miscible with the paclitaxel solvent to form a solution which is then emulsified with the paclitaxel solution, or (iii) added as solid particulates to the paclitaxel solution. The solution, emulsion, or suspension of the pore forming agent in the paclitaxel solution then is further processed to remove

the paclitaxel solvent, the pore forming agent, and, if appropriate, the solvent for the pore forming agent simultaneously or sequentially using evaporation, spray drying, fluid bed drying, lyophilization, vacuum drying, or a combination of these techniques.

In a preferred embodiment, the solid pore forming agent is a volatile salt, such as salts of volatile bases combined with volatile acids. Volatile salts are materials that can transform from a solid or liquid to a gaseous state using added heat and/or vacuum. Examples of volatile bases include ammonia, methylamine, ethylamine, dimethylamine, diethylamine, methylethylamine, trimethylamine, triethylamine, and pyridine. Examples of volatile acids include carbonic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, formic acid, acetic acid, propionic acid, butyric acid, and benzoic acid. Preferred volatile salts include ammonium bicarbonate, ammonium acetate, ammonium chloride, ammonium benzoate and mixtures thereof.

Other examples of solid pore forming agents include iodine, phenol, benzoic acid (as acid not as salt), and naphthalene.

The solid pore forming agent is used in an amount between 0.5 and 1000% (w/w), preferably between 1 and 600% (w/w), and more preferably between 1 and 100% (w/w), of the paclitaxel.

IV. Method of Making the Porous Paclitaxel Matrix

The paclitaxel matrices preferably are made by (i) dissolving paclitaxel in a volatile solvent to form a paclitaxel solution, (ii) combining at least one pore forming agent with the paclitaxel solution to form an emulsion, suspension, or second solution, and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution. In a preferred embodiment, spray drying, optionally followed by lyophilization or vacuum drying, is used to remove the solvents and the pore forming agent. The removal of the pore forming agent can be conducted simultaneously with or following removal of enough solvent to solidify the droplets. Production can be carried out using continuous, batch, or semi-continuous processes.

First, paclitaxel is dissolved in an appropriate solvent. The concentration of the paclitaxel in the resulting paclitaxel solution typically is between about 0.01 and 80% (w/v), preferably between about 0.025 and 30% (w/v).

Next, the paclitaxel solution is combined, typically under mixing conditions, with the pore forming agent or solution thereof. If a liquid pore forming agent is used, it is first emulsified with the paclitaxel solution to form droplets of pore forming agent dispersed throughout the paclitaxel solution. If a solid pore forming agent is used, it is dissolved either directly in the paclitaxel solution to form a solution of paclitaxel/pore forming agent, or it is first dissolved in a second solvent. If the second solvent is immiscible with the paclitaxel solvent, the solution of the pore forming agent is emulsified with the paclitaxel solution to form droplets of the pore forming agent solution dispersed throughout the paclitaxel solution. If the second solvent is miscible with the paclitaxel solution, the two solutions are mixed to form a single solution. A solid pore forming agent alternatively can be added directly to the paclitaxel solution as solid particulates, preferably between about 10 nm and 10 μm in size, to form a suspension of pore forming agent in the paclitaxel solution. Subsequently, the solid pore forming agent particle size can be reduced by further processing the resulting suspension, for example, using homogenization or sonication techniques known in the art.

Then, the solution, emulsion, or suspension is further processed to remove the paclitaxel solvent and the pore forming agent simultaneously or sequentially, using evaporation, spray drying, fluid bed drying, lyophilization, vacuum drying, or a combination of these techniques. In a preferred embodiment, the solution, emulsion, or suspension is spray-dried. As used herein, "spray dry" means to atomize the solution, emulsion, or suspension to form a fine mist of droplets (of paclitaxel solution having solid or liquid pore forming agent dispersed throughout), which immediately enter a drying chamber (e.g., a vessel, tank, tubing, or coil) where they contact a drying gas. The solvent and pore forming agents evaporate from the droplets into the drying gas to solidify the droplets, simultaneously forming pores throughout the solid. The solid (typically in a powder, particulate form) then is separated from the drying gas and collected.

The temperature of the inlet and outlet ports of the drying chamber, as well as the flow rates of the feed solution, atomization gas, and drying gas, can be controlled to produce the desired products. In a particularly preferred embodiment, the spray drying methods described in U.S. Pat. No. 5,853,698 to Straub et al., which is hereby incorporated by reference, are adapted to make the paclitaxel matrices described herein.

The paclitaxel present in the solids or powder produced may be in a crystalline or an amorphous state, or may be mixture of such states. The state generally depends on how the droplets are dried and the excipients present.

Emulsion Stabilization

In embodiments in which at least one pore forming agent is combined with the paclitaxel solution to form an emulsion, a surfactant or emulsifying agent can be added to enhance the stability of the emulsion. A variety of surfactants may be incorporated in this process, preferably to an amount between 0.1 and 5% by weight. Exemplary emulsifiers or surfactants which may be used include most physiologically acceptable emulsifiers, for instance egg lecithin or soya bean lecithin, or synthetic lecithins such as saturated synthetic lecithins, for example, dimyristoyl phosphatidyl choline, dipalmitoyl phosphatidyl choline or distearoyl phosphatidyl choline or unsaturated synthetic lecithins, such as dioleyl phosphatidyl choline or dilinoleyl phosphatidyl choline. Other hydrophobic or amphipathic compounds can be used in place of the phospholipid, for example, cholesterol. Emulsifiers also include surfactants such as free fatty acids, esters of fatty acids with polyoxyalkylene compounds like polyoxypropylene glycol and polyoxyethylene glycol; ethers of fatty alcohols with polyoxyalkylene glycols; esters of fatty acids with polyoxyalkylated sorbitan; soaps; glycerol-polyalkylene stearate; glycerol-polyoxyethylene ricinoleate; homo- and co-polymers of polyalkylene glycols; polyethoxylated soya-oil and castor oil as well as hydrogenated derivatives; ethers and esters of sucrose or other carbohydrates with fatty acids, fatty alcohols, these being optionally polyoxyalkylated; mono-, di- and tri-glycerides of saturated or unsaturated fatty acids, glycerides of soya-oil and sucrose.

Other emulsifiers include natural and synthetic forms of bile salts or bile acids, both conjugated with amino acids and unconjugated such as taurodeoxycholate and cholic acid.

V. Paclitaxel Matrix Applications

The paclitaxel matrices described herein are useful in formulations for administration to a patient in need of the paclitaxel. As used herein, "patient" refers to animals, including mammals, preferably humans. The porous matrices or formulations thereof are suitable for administration of the paclitaxel by a variety of routes, for example, parenteral, mucosal, oral, topical/transdermal administration, for local, regional, or systemic effect. Examples of parenteral routes

include intravenous, intrarterial, intracardiac, intrathecal, intraosseous, intraarticular, intrasynovial, intracutaneous, subcutaneous, and intramuscular. Examples of mucosal routes include pulmonary (intrarespiratory), buccal, sublingual, intranasal, rectal, and vaginal administration. The porous matrices can be formulated for intraocular, conjunctival, aural, urethral, intracranial, intralesional, and intratumoral administration.

In a preferred embodiment, the paclitaxel matrix is in the form of powder, which can be reconstituted with an aqueous medium, such as physiological saline, and administered parenterally, such as intramuscularly, subcutaneously, or intravenously. An advantage of the formulations described herein is that they can be used to convert paclitaxel which must be infused (e.g., to avoid precipitation of the paclitaxel following bolus injection) to a bolus formulation, avoiding unacceptable precipitation of paclitaxel in vivo or for local delivery.

Alternatively, the matrix can be further processed using standard techniques into tablets or capsules for oral administration. These techniques are described, for example, in Ansel, et al., "Pharmaceutical Dosage Forms and Paclitaxel Delivery Systems," 6th Ed., (Williams & Wilkins 1995), which is incorporated herein by reference.

The present invention will be further understood with reference to the following non-limiting examples.

Overview

Examples 1-2 demonstrate production of paclitaxel matrices using different wetting agents and different solvents.

Examples 3-4 describe the analyses which were used to characterize the porous paclitaxel matrices produced in Examples 1-2. These characteristics include density and dissolution properties.

Example 6 describes the antitumor activity of the paclitaxel formulation produced in example 5 in female athymic NCr-nu mice in which the MDA-MB 435 breast tumor has been implanted subcutaneously (sc).

Materials and Equipment

The following materials and equipment were used in the examples. PEG 3350, polyvinylpyrrolidone K-15, TWEEN™ 80, and ammonium bicarbonate, were obtained from Spectrum Chemicals (Gardena, Calif.). Paclitaxel was obtained from Hauser (Boulder, Colo.). Methylene chloride was obtained from EM Science (Gibbstown, N.J.). All emulsions were produced using a Virtis IQ^2 homogenizer (Virtis, Gardiner, N.Y.). Formulations were spray dried on a benchtop spray dryer using an air atomizing nozzle.

Example 1

Production of a Porous Paclitaxel Matrix Using Ammonium Bicarbonate as a Pore Forming Agent

A paclitaxel-loaded organic solution was prepared by dissolving 1.0 g of paclitaxel, 0.10 g of TWEEN™ 80, and 0.10 g of polyvinylpyrrolidone K-15 in 160 ml of ethanol. An aqueous solution composed of 0.42 g of ammonium bicarbonate and 1.0 g of mannitol in 40 ml of DI water was added to the ethanol solution and mixed. The resulting 80% ethanol solution was spray dried on a benchtop spray dryer using an air-atomizing nozzle and nitrogen as the drying gas. Spray drying conditions were as follows: 20 ml/min solution flow rate, 60 L/min atomization gas rate, 100 kg/hr drying gas rate, and 55° C. outlet.

Example 2

Production of a Porous Paclitaxel Matrix Using Ammonium Bicarbonate as a Pore Forming Agent

A paclitaxel-loaded organic solution was prepared by dissolving 0.4 g of paclitaxel, 0.10 g of TWEEN™ 80, and 0.04 g of polyvinylpyrrolidone K-15 in 160 ml of ethanol. An aqueous solution composed of 0.30 g of ammonium bicarbonate and 1.0 g of mannitol in 40 ml of DI water was added to the ethanol solution and mixed. The resulting 80% ethanol solution was spray dried on a benchtop spray dryer using an air-atomizing nozzle and nitrogen as the drying gas. Spray drying conditions were as follows: 20 ml/min solution flow rate, 60 L/min atomization gas rate, 100 kg/hr drying gas rate, and 55° C. outlet temperature.

Example 3

In Vitro Dissolution of Porous Paclitaxel Matrices

The in vitro dissolution rates of the powders produced in Examples 1-2 were compared to the dissolution rates of the non-formulated paclitaxel.

Analytical Methods

Studies were conducted in PBS containing 0.08% TWEEN™ 80 (T80/PBS). T80/PBS (10 mL) was added to an appropriate amount of material being tested to contain 5 mg of paclitaxel in a 15 mL polypropylene conical tube, and the suspension was vortexed for 3-4 minutes. The suspension (0.25 mL) was then added to 250 mL of T80/PBS in a 600 mL glass beaker for dissolution analysis. All dissolution studies were conducted using overhead mixing. The mixer used was an IKARW16 Basic Mixer with a R1342 impeller shaft running at stirring rate 5. Samples were removed via pipette, filtered through 0.22 micron CA syringe filter, and then analyzed. Dissolution curves are presented as percent of complete dissolution.

HPLC analysis was performed directly on the filtered aqueous solutions using High Pressure Liquid Chromatography ("HPLC") (Hewlett Packard Series 1100 HPLC). The chromatographic conditions included a Nucleosil column (5:m, C18, 100A, 250×4.6 mm), a mobile phase of 2 mM H_3PO_4/Acetonitrile (2:3) at a flow rate of 1.5 mL/min, UV detection at 227 nm, and a run time of 25 min.

Results

The in vitro dissolution rates of the porous paclitaxel matrices produced in examples 1-2 are provided in FIG. **1**. The in vitro dissolution of the porous paclitaxel matrices are compared to the bulk paclitaxel of interest. In all cases, the time for 80% dissolution of the porous paclitaxel matrices is greater than 1000 times shorter than the time for 80% of the bulk paclitaxel to dissolve. The rate of dissolution which is approximated as the slope of the curve is greater than 1000 times greater for the porous paclitaxel matrices of Examples 1-2 as compared to the specific bulk paclitaxel of interest.

Example 4

Density of Porous Paclitaxel Matrices

The densities of the dry powder produced in Examples 1-2 are summarized in Table 1. Density was measured using Transaxial Pressure ("TAP") with a Micromeritics GeoPyc 1360 using a consolidation force of 8 Newtons. The density of the porous matrices is less than 1.0 g/mL for Examples 1-2.

TABLE 1

Particle Density Analysis

Material	Density (g/mL)
Example 1	0.67
Example 2	0.52

Example 5

Production of a Porous Paclitaxel Matrix For Testing in Animal Tumor Model

A paclitaxel-loaded organic solution was prepared by dissolving 2.0 g of paclitaxel, 0.20 g of polyvinylpyrrolidone, and 0.20 g of TWEEN™ 80 in 320 ml of ethanol. An aqueous solution composed of 0.85 g of ammonium bicarbonate and 2.0 g of mannitol in 80 ml of DI water was added to the organic solution (phase ratio 1:4). Prior to spray drying, the solution was filtered through a 0.22 μm PVDF membrane. A benchtop spray dryer using an air-atomizing nozzle and nitrogen as the drying gas were used. Spray drying conditions were as follows; 20 ml/min solution flow rate, 60 L/min atomization gas rate, 100 kg/hr drying gas rate, and 54° C. outlet temperature.

Example 6

Testing of Porous Paclitaxel Matrix in Animal Efficacy Model

The antitumor activity of the paclitaxel formulation produced in Example 5 was tested in female athymic NCr-nu mice in which the MDA-MB 435 breast tumor has been implanted subcutaneously (sc), using doses of 7.5, 15, 30, and 45 mg/kg. Mice were implanted subcutaneously with 30-40 mg fragments of the MDA-MB 435 tumor on Day 0. Treatment with the porous paclitaxel matrix began when the tumors ranged in size from 75-150 mg. Two control groups were included, a vehicle-treated control group and a TAXOL™ treated group. The dose of the TAXOL™ treated group was set at the maximum tolerated dose in this animal model. Treatment was administered once a day intravenously for five days. Mice were observed daily for survival. Tumor measurements were recorded twice weekly. Tumors were measured in two dimensions using calipers and converted to tumor mass using the volume of a prolate ellipsoid and assuming unit density. Median tumor mass for the various groups in shown in FIG. **2** plotted as a function of the day, with day 0 being the first day of dosing. There was no tumor regression in the dextrose vehicle control group. The administration of the porous paclitaxel matrix lead to a dose dependent regression in tumor mass with tumor masses below the limit of detection at the highest dose by day 6. The porous paclitaxel matrix therefore allows for elimination of Cremophor and ethanol and thus higher total doses of paclitaxel were administered. The higher dose porous paclitaxel matrix groups had a more rapid rate of tumor regression and smaller tumor mass.

Modifications and various of the present invention will be obvious to those of skill in the art from the foregoing detailed description. Such modifications and various are intended to come within the scope of the following claims.

We claim:

1. A pharmaceutical composition comprising a porous matrix formed of a hydrophilic excipient, a wetting agent and nanoparticles and microparticles of a taxane, wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5 μm and a total surface area greater than about [0.5 m^2] *0.5 m^2/mL*, wherein the porous matrix is in a dry powder form, and wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles, wherein the dissolution rate of the taxane nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed taxane.

2. The composition of claim **1**, wherein the matrix is made by a process comprising (a) dissolving a taxane in a volatile solvent to form a taxane solution, (b) combining at least one pore forming agent, a wetting agent, and a hydrophilic excipient with the taxane solution to form an emulsion, suspension, or second solution, and (c) removing the volatile solvent and the pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix.

3. The composition of claim **2** wherein the pore forming agent is a volatile salt.

4. The composition of claim **1** wherein the porous matrix is in a dry powder form having a TAP density less than or equal to 1.0 g/mL.

5. The composition of claim **1**, wherein the matrix comprises at least one excipient selected from the group consisting of hydrophilic polymers, sugars, tonicity agents, pegylated excipients, and combination thereof.

6. The composition of claim **1** wherein the mean diameter of the taxane microparticles is between about 0.50 and 5 μm.

7. A taxane suspension comprising the composition of claim **1** added to an aqueous solution suitable for parenteral administration.

8. The composition of claim **1** wherein the matrix is processed into tablets or capsules suitable for oral administration.

9. The composition of claim **1** wherein the matrix is formed into suppositories suitable for vaginal or rectal administration.

10. The composition of claim **1** wherein the matrix is in a dry powder form suitable for pulmonary administration.

11. A method for making a porous matrix of a taxane comprising (a) dissolving a taxane in a volatile solvent to form a taxane solution, (b) combining at least one pore forming agent, a wetting agent, and a hydrophilic excipient with the taxane solution to form an emulsion, suspension, or second solution, and (c) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix comprising nanoparticles and microparticles of taxane, wherein the dissolution rate of the taxane nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed taxane.

12. The method of claim **11** wherein the wetting agent is a polyoxyethylene sorbitan fatty acid ester.

13. The method of claim **11** wherein step (c) is conducted using a process selected from spray drying, evaporation, fluid bed drying, lyophilization, vacuum drying, or a combination thereof.

14. The method of claim **11** wherein the taxane solution or pore forming agent comprises excipients selected from the group consisting of hydrophilic excipients, pegylated excipients, and tonicity agents.

15. The method of claim **11** wherein the pore forming agent is a volatile salt.

16. The method of claim **15** wherein the volatile salt is selected from the group consisting of ammonium

bicarbonate, ammonium acetate, ammonium chloride, ammonium benzoate, and mixtures thereof.

17. A method of treating a patient with a taxane, comprising administering to a patient in need thereof a therapeutically or prophylactically effective amount of a taxane *to provide anticancer or antitumor activity* in a formulation comprising a porous matrix formed of a hydrophilic excipient, a wetting agent and nanoparticles and microparticles of a taxane, wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5 μm and a total surface area greater than about 0.5 m^2/mL, and wherein the porous matrix is in a dry powder form having a TAP density less than or equal to 1.0 g/mL wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles wherein the dissolution **[**rare**]** *rate* of the taxane nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed taxane.

18. The method of claim **17** wherein the formulation is suitable for administration by a route selected from the group consisting of parenteral, mucosal, oral, and topical administration.

19. The method of claim **18** wherein the parenteral route is selected from the group consisting of intravenous, intraarterial, intracardiac, intrathecal, intraosseous, intraarticular, intrasynovial, intracutaneous, subcutaneous, and intramuscular administration.

20. The method of claim **18** wherein the mucosal route is selected from the group consisting of pulmonary, buccal, sublingual, intranasal, rectal, and vaginal administration.

21. The method of claim **18** wherein the formulation is suitable for intraocular or conjunctival administration.

22. The method of claim **18** wherein the formulation is suitable for intracranial, intralesional, or intratumoral administration.

23. The method of claim **18** wherein the formulation is in an aqueous solution suitable for parenteral administration.

24. The method of claim **18** wherein the formulation is in a tablet or capsule suitable for oral administration.

25. The method of claim **18** wherein the formulation is in a suppository suitable for vaginal or rectal administration.

26. The method of claim **18** wherein the formulation is a dry powder suitable for pulmonary administration.

27. The composition of claim **1** wherein the taxane is paclitaxel.

28. The method of claim **11** wherein the taxane is paclitaxel.

29. The method of claim **17** wherein the taxane is paclitaxel.

30. The composition of claim **1** wherein the hydrophilic excipient is selected from the group consisting of water soluble polymers and sugars, and the wetting agent is a surfactant.

31. The method of claim **11** wherein the hydrophilic excipient is selected from the group consisting of water soluble polymers and sugars, and the wetting agent is a surfactant.

32. The method of claim **17** wherein the hydrophilic excipient is selected from the group consisting of water soluble polymers and sugars, and the wetting agent is a surfactant.

33. A method for making a porous matrix comprising nanoparticles and microparticles of paclitaxel, the method comprising (a) dissolving paclitaxel in a volatile solvent to form a paclitaxel solution, (b) combining at least one pore forming agent including ammonium bicarbonate, a polyoxyethylene sorbitan fatty acid ester, and polyvinylpyrrolidone with the paclitaxel solution to form an emulsion, suspension, or second solution, and (c) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix comprising nanoparticles and microparticles of paclitaxel, wherein the dissolution rate of the paclitaxel nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed paclitaxel.

34. The method of claim 33, wherein the polyoxyethylene sorbitan fatty acid ester is polysorbate 80.

35. The method of claim 33, wherein step (b) further comprises adding a sugar to the paclitaxel solution.

36. The method of claim 35, wherein the sugar is mannitol.

37. A pharmaceutical composition comprising a porous matrix formed of polyvinylpyrrolidone, a polyoxyethylene sorbitan fatty acid ester and nanoparticles and microparticles of paclitaxel,

wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5 μm and a total surface area greater than about 0.5 m^2/mL, wherein the porous matrix is in a dry powder form, and wherein upon exposure to an aqueous medium, the matrix dissolves to leave the paclitaxel nanoparticles and microparticles, wherein the dissolution rate of the paclitaxel nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed paclitaxel.

38. The composition of claim 37, wherein the polyoxyethylene sorbitan fatty acid ester is polysorbate 80.

39. The composition of claim 37, further comprising a sugar.

40. The composition of claim 39, wherein the sugar is mannitol.

41. A method of treating a patient with a paclitaxel formulation, comprising administering to a patient in need thereof a therapeutically or prophylactically effective amount of paclitaxel to provide anticancer or antitumor activity in a formulation comprising a porous matrix formed of polyvinylpyrrolidone, a polyoxyethylene sorbitan fatty acid ester and nanoparticles and microparticles of paclitaxel, wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5 μm and a total surface area greater than about 0.5 m^2/mL, and wherein the porous matrix is in a dry powder form having a TAP density less than or equal to 1.0 g/mL, wherein upon exposure to an aqueous medium, the matrix dissolves to leave the paclitaxel nanoparticles and microparticles wherein the dissolution rate of the paclitaxel nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed taxane.

42. The method of claim 41, wherein the polyoxyethylene sorbitan fatty acid ester is polysorbate 80.

43. The method of claim 41, wherein the formulation further comprises a sugar.

44. The method of claim 43, wherein the sugar is mannitol.

45. The composition of claim 1, wherein the hydrophilic excipient is the wetting agent.

46. The method of claim 11, wherein the hydrophilic excipient is the wetting agent.

47. The method of claim 17 wherein the hydrophilic excipient is the wetting agent.

* * * * *

CERTIFICATE OF SERVICE

I hereby certify that on July 7, 2014, I caused the foregoing Brief of Plaintiffs-Appellants to be electronically filed with the Clerk of Court using the CM/ECF system, and thereby served via CM/ECF on counsel for Defendants-Cross-Appellants.

Dated: July 7, 2014

/s/ George C. Lombardi
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CERTIFICATE OF COMPLIANCE
WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 28.1(e)(2) because it contains 10,169 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and Fed. Cir. R. 32(b).

2. This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because it has been prepared in 14-point Century Schoolbook, a proportionally spaced typeface, using Microsoft Word 2010.

Dated: July 7, 2014

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